FDA Executive Summary

Prepared for the April 24, 2014 meeting of the Neurological Devices Panel

Electrical Stimulation Devices for Aversive Conditioning

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1 Introduction

FDA is considering issuing a ban on electrical stimulation devices (ESDs) for aversive conditioning that are intended to deliver a noxious electrical stimulus to patients exhibiting self-injurious behavior (SIB) and aggressive behavior.[1] This includes only devices under the Aversive Conditioning Devices regulation (Class II, 21 CFR 882.5235[2]).

Aversive conditioning devices were on the market prior to passage of the Medical Device Amendments on May 28, 1976. In 1979, they were classified as Class II devices, regulated under the premarket notification (510(k)) process (Section 3.1). FDA has conducted a comprehensive review of the available information regarding ESDs for SIB and aggressive behavior, and is concerned that they may present a substantial and unreasonable risk of illness or injury. Therefore, FDA is considering banning these devices under section 516 of the FD&C Act.

FDA is convening this Advisory Panel meeting to seek scientific and clinical expert opinion on the risks and benefits associated with other treatment options, the risks and benefits of ESDs for aversive conditioning, and on whether these devices present a substantial and unreasonable risk of illness or injury. The Center for Devices and Radiological Health (CDRH) has previously banned one device, prosthetic hair fibers.[3]

To help in your assessment of the questions that will help inform whether the FDA should ban ESDs for aversive conditioning, this document presents the following information,

- Section 2 - Banning Criteria: provides the criteria for banning a device;
- Section 3 - Regulatory History: provides a discussion of the regulatory history and a description of the device technology;
- Section 4 - Clinical Background Information: provides an overview of self-injurious behaviors and aggressive behaviors, in persons with intellectual and developmental disabilities and the benefits and risks associated with alternative treatments;
- Section 5 - Benefits and Risks of ESDs for Aversive Conditioning: provides the results of FDA's systematic review of the scientific literature and other additional information with respect to the risks and benefits associated with these devices;
- Section 6 - Ethical Considerations with Particular Focus on Issues Related to Clinical Studies: provides a discussion of the ethical considerations with particular focus related to clinical studies with the device; and
- Section 7 – Summary: provides a summary of information contained in this Executive Summary and the context for which the panel will be asked questions.

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[1] FDA is not seeking input from the Panel regarding ESDs for other indications (e.g., smoking cessation and nail biting) because they involve fundamentally different patient populations with different potential risks and benefits that do not raise the same concerns.

[2] 21 CFR 882.5235, "An aversive conditioning device is an instrument used to administer an electrical shock or other noxious stimulus to a patient to modify undesirable behavioral characteristics."

[3] See 21 CFR 895.101; 48 FR 25126, 49 FR 1177.

2 Banning Criteria

2.1 FDA Authority to Ban Devices

Section 516 of the Federal Food, Drug, and Cosmetic Act (the Act) authorizes FDA to ban, by regulation, any device intended for human use that "presents substantial deception or an unreasonable and substantial risk of illness or injury."[4] We are seeking Panel input related to the "unreasonable and substantial risk of illness or injury" component of the banning standard; we are not asking the Panel any questions related to "substantial deception."

FDA regulations provide that, when determining whether risk of illness or injury is "substantial," FDA will consider whether it is important, material, or significant in relation to the device's benefit to the public health.[5] Actual proof of injury to consumers is not required.[6] Although FDA's banning regulations do not set forth a standard for "reasonableness," the agency in the past has explained that, to determine the reasonableness of a risk associated with use of a device, it will analyze that risk relative to the state of the art and the potential hazard to patients and users.[7]

2.2 Evidence to Ban a Medical Device

The statute and regulations require FDA to consider "all available data and information" in making a banning determination.[8] This information can include data obtained under other provisions of the Act, information supplied by manufacturers, and any other information submitted voluntarily.[9]

2.3 Labeling Requirements

Before banning a device, FDA must make a specific determination that the substantial deception or unreasonable and substantial risk cannot be eliminated by a change in the labeling for the device. According to the statute, if FDA finds that the deception or risk can be corrected or eliminated through labeling, FDA must notify the manufacturer of the need for revised labeling and provide a specified period for the manufacturer to implement the revision.[10] For instance, FDA can require labeling to include a specific statement, notice, or warning presented in a specific manner and form.[11] If the manufacturer fails to implement the change within the period specified by FDA, the agency may initiate the banning process.

2.4 Applicability of the Ban to Devices in Distribution and Use

If FDA decides to proceed with banning these devices, it must determine whether to apply the ban to devices already in commercial distribution, to those already sold to the ultimate

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[4]   21 U.S.C. § 360f (a).
[5]   21 CFR § 895.21(a)(1).
[6]   44 FR 29215.
[7]   Id.
[8]   21 U.S.C. § 360f(a); 21 CFR § 895.21(a)(3)
[9]   21 CFR § 895.21(a)(3)
[10] 21 U.S.C. § 360f(a)(2); *see also* 21 C.F.R. § 895.21(c)
[11] 21 C.F.R. § 895.25(b).

user, both, or neither. In other words, FDA may limit the ban only to devices in future distribution or it may also apply the ban to devices already in commercial distribution but not yet in use by patients, or it may also apply the ban to already being used by patients.

2.5   Banning Process

In order to ban a device, FDA must go through notice and comment rulemaking, which requires a proposed rule, consideration of comments, and a final rule.[12]   Before initiating the banning process, FDA may consult with the relevant expert panel of the Medical Device Advisory Committee.[13]   FDA may declare a proposed regulation to be effective upon its date of publication in the Federal Register if the Agency (1) determines that the deception or risk of illness or injury presents an unreasonable, direct, and substantial danger to the health of individuals, and (2) notifies the manufacturers of the device of this special effective date prior to publication of the proposed rule and provides an opportunity for an informal hearing on the proposed regulation.[14]   This special effective date procedure may be used when FDA determines the potential or actual injury involved is a serious one that FDA believes will endanger the health of individuals who have been, or will be, exposed to the device.[15]   FDA need not find that the danger is immediate; it is sufficient that the danger may involve a serious long term risk.[16]

3 Regulatory History

3.1 Device Classification

Aversive conditioning devices were on the market prior to passage of the Medical Device Amendments on May 28, 1976. As such, these devices were included in FDA's original device classification efforts. As discussed in the proposed rule for the original classification of these devices,[17] the originally identified risks to health associated with aversive conditioning devices were,

- Worsened psychological condition - The patient's mental condition may become worse if aversive conditioning is administered incorrectly or if the patient is not carefully selected for this treatment.
- Electrical shock - Leakage current from the device may injure the patient.
- Patient injury - An aversive shock applied to the patient may be harmful or lethal if excessive current is used or if it is applied incorrectly.

The proposed rule also cited four literature references (Butterfield (1975), Johnson (1970), Logan and Turnage (1975), and Thorne (1975)). The original Neurological Device Classification Panel recommended that aversive conditioning devices be classified into Class

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[12]   21 U.S.C. § 360f(a); 21 CFR § 895.21.
[13]   21 CFR § 895.21(b).
[14]   21 U.S.C. § 360f(b); 21 CFR § 895.30.
[15]   21 CFR § 895.30(b).
[16]   Id.
[17]   43 FR 55705, November 28, 1978

II, because the Panel believed that the electrical hazards associated with use of the device could be managed with performance standards. FDA concurred with the Panel's recommendation and, after receiving no comments on the proposed rule, the classification was finalized in 1979[18]. Aversive conditioning devices were identified in the classification regulation (21 CFR part 882.5235) as *"an instrument used to administer an electrical shock or other noxious stimulus to a patient to modify undesirable behavioral characteristics"* [Class II (performance standards)].

As Class II devices, aversive conditioning devices are regulated under the premarket notification (510(k)) process. Premarket notification requires that new or significantly modified devices being introduced into the U.S. market show only that they are "substantially equivalent" to an existing legally marketed (e.g., "predicate") device of the same type. The 510(k) process involves a comparison of a new device to a predicate device rather than an independent demonstration of the new device's safety and effectiveness.

3.2   510(k) Cleared Devices

3.2.1   Cleared Devices and Indications for Use

The first 510(k)-cleared aversive conditioning device was cleared in 1976 using a device marketed prior to the Medical Device Amendments as a predicate device. Subsequent to this clearance, five other devices received clearance under this classification. Table 1 describes the four cleared devices that are generally indicated to treat self-injurious behavior (SIB) in patients that are usually diagnosed as autistic or with intellectual and developmental disabilities. These devices are cleared as prescription devices, which means that federal law requires sale of the devices be by or pursuant to, the order of a professional licensed by the law of the State in which he or she practices.

The two other devices that were cleared under this device regulation are for use in smoking cessation and nail biting (510(k) document numbers K790738 and K820622). However, the FDA is not seeking input from the Panel regarding smoking cessation and nail biting because they present fundamentally different patient populations with different potential risks and benefits that do not raise the same concerns.

To the best of FDA's knowledge, there is currently only one entity in the United States (the Judge Rotenberg Center in Massachusetts) that has recently manufactured and is currently using ESDs for aversive conditioning. JRC is currently using devices (the GED-3A and GED-4) that have been modified from the FDA cleared device and have not received FDA clearance or approval, in violation of the FD&C Act. The GED-4 has an average output current that is almost three times that of the FDA cleared GED device (Israel et al., 2008). The ban that FDA is considering would apply to these devices as well as the FDA-cleared ESDs.

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[18]   44 FR 51765, September 4, 1979

Table 1: FDA Cleared ESDs for Aversive Conditioning for the Treatment of SIB

510(k) Number	Device	Clearance Date	Cleared Indications for Use
K760166	Stimulator Sonic Control (WS-1) "Whistle Stop" Farrall Instruments Inc.	7/20/76	"As an aid in modifying unacceptable behavior which is socially or physically injurious to the client. It is to be used only where an ethical treatment design in which the eventual goal of therapy is to eliminate the undesired behavior and the use of shock is strictly followed. The device is not for sale to control people."
K853178	SIBIS [Self-Injurious Behavior Inhibiting System] Oxford Medilog, Inc.	2/28/86	"For the treatment of retarded or autistic clients who exhibit head-banging behavior of sufficient intensity and frequency to cause acute or chronic physical damage. The device should be used only in patients where other forms of therapy have been attempted and failed."
K871158	SIBIS Remote Actuator Human Tech. Inc.	5/29/87	"To treat self-injurious behavior that does not involve blows to the head sufficient to trigger the acceleration sensor. Some examples are eye gouging, skin pinching, hair pulling, and jaw banging."
K911820	GED [Graduated Electronic Decelerator] Judge Rotenberg Educational Center	12/5/94	"For the treatment of patients, usually diagnosed as retarded or autistic, who exhibit self-injurious behavior of sufficient intensity and frequency to cause serious damage to themselves. The device should be used only on patients where alternate forms of therapy have been attempted and failed."

3.2.2 Technological Characteristics of Cleared Devices

As discussed in Section 3.2.1 above, the FDA has cleared four ESDs for aversive conditioning for the treatment of SIB. The main components of these devices are an electrical stimulus ("shock") generation module, cutaneous electrodes, and either a remote monitor module or an automatic mechanism to trigger a stimulus to be applied to the patient. The stimulus generation module is carried by the patient via a waist or back pack, and the electrodes are attached to the patient's skin. The remote monitor emits a radio signal that is uniquely coded to a specific generator module and is controlled by a trained practitioner who determines when it is appropriate to deliver

an electrical shock to the patient. An example of a device with an automatic trigger is the SIBIS (Self-Injurious Behavior Inhibiting System) device (K853178) in which an acceleration sensor module is placed in a headband worn by the patient. When the sensor detects a blow to the head that is sufficient enough, it triggers an electrical stimulus to be applied to electrodes placed on the patient's body.
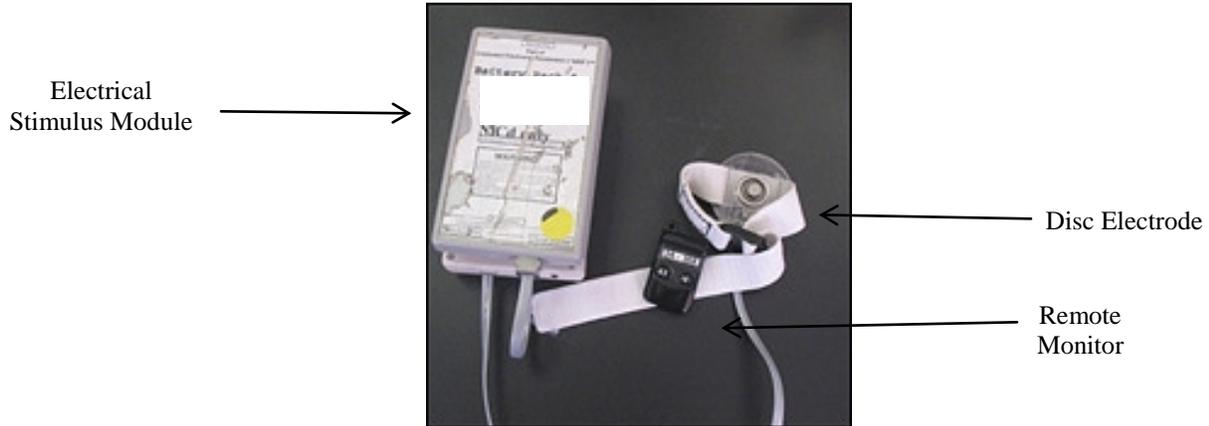

Figure 1: GED Electrical Stimulus Generation Module and Remote Monitor
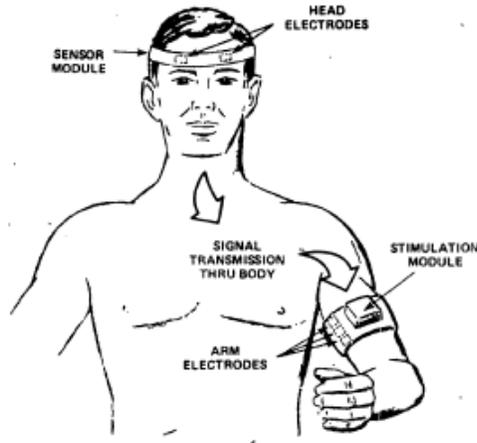
Figure 2: SIBIS System Cleared under K853178

The electrical shock delivered to the patient varies in intensity and location among the various cleared devices as shown in Table 2 below. Please refer to Section 3.3 for a discussion of how the various output parameters can affect pain perception.

Table 2: Output Stimulus Parameters and Electrodes for FDA Cleared ESDs for Aversive Conditioning for the Treatment of SIB

Device	Output Stimulus Parameters[1]	Electrodes	Electrode Location(s) Per Instructions for Use[1]
"Whistle Stop" (K760166)	Maximum Current, 10 mA @ 20 kΩ Maximum Voltage, 200V Frequency, 10 Hz Pulse Width, 1-2 ms Maximum Power Density, 0.02 W/cm^2 Biphasic Waveform Shock Duration, 0.5-12 s	Dual Button Electrodes	On one leg or one arm. About 1" apart.
SIBIS (K853178 and K871158)	Maximum Current, 10 mA (no load specified) Average (rms) Current, 3.5 mA @ 20kΩ Maximum Voltage, 200V Frequency, 20kHz signal modulated at 80 Hz Pulse Width, 6.2 ms Maximum Power Density, 0.16 W/cm^2 Biphasic Waveform Shock Duration, 0.1-0.2 s	Concentric ring Electrode Ring Surface Area (SA), 1.81 cm^2 Button SA, 0.19 cm^2	Uses a sensor module of the head to provide stimulation on the arms.[2]
GED (K911820)	Maximum Current, 29.4 mA @ 5 kΩ Average (rms) Current, 12 mA @ 5 kΩ Maximum Voltage, 150 V Frequency, 80 Hz Pulse Width, 3.125 ms Maximum Avg. Power Density, 1.01 W/cm^2 @ 5 kΩ Monophasic Waveform Shock Duration, 2 s	Concentric ring Ring SA, 0.7 cm^2 or Dual Button Electrodes (placed ≤ 6" apart) SA = 0.7 cm^2	On the extremities, such as the inner or outer surface of an arm or leg, or the feet bottoms or palm of the patient. It may also be placed on the upper three quarters-of the buttocks and the lower back, or the right side on the upper chest or back.[3]

[1] As reported in FDA 510(k) submission. Note that the average power density is associated with the potential for skin burns. This safety parameter was assessed in the FDA review of these devices.

[2] Warnings include to never place electrodes on the chest or head and to never place electrodes to allow current flow through the chest.

[3] Warnings include the following, never place the electrode on the patient so that the stimulus current could pass through the chest cavity and never place the electrode on the chest or breasts, genitals, head, top of hand, top of foot, the lower quadrant of the buttocks of a patient, or on any area of skin known to be unusually sensitive in that patient to skin irritation or subject to allergic reaction in that patient to contact with stainless steel. Instructions are also provided to inspect the skin under the electrode frequently and no less than every 6 hour period of use and to inspect more frequently in cases of frequent stimulus application or as indicated by a patient's prior history of skin irritation.

3.3   ESDs for Aversive Conditioning and Pain Perception

This section describes how different device characteristics can affect the perception of pain created by ESDs for aversive conditioning and how this perception may vary among individuals treated with the ESDs. It should be noted that patient impressions induced by electrical stimulation provide a uniqueness that may not be observed with other types of

aversive stimuli. That is, electrical stimuli applied to the same sensory location can give a cutaneous sensation of intensity (e.g., touch, prick, itch, or sharp pain) but also can provide an emotional or affective feeling of discomfort or unpleasantness (e.g., intolerable, agonizing, horrible, etc.) (Delitto et al, 1992; Tashiro and Higashiyama, 1981). Determining the degree to which ESDs for aversive conditioning can cause certain levels of pain intensity and unpleasantness is challenging and the purpose of this section is to explain this complexity by describing some of the known device and individual patient characteristics that have been shown to affect shock perceptions.

It should be noted that the data provided below is based on studies of individuals without disabilities. In an article by Allely (2013) the author states that there is a widely held belief in the peer reviewed literature that individuals with Autistic Spectrum Disorder (ASD)are insensitive to pain or have a high pain threshold . However, the author challenges this belief and instead propose that there is a strong possibility that not all children with ASD express their pain in the same way as a "neurotypical child" would (e.g., cry, moan, seek comfort, etc.), which may lead to misinterpretation by caregivers and medical professionals that patents are insensitive or to an incorrect belief that the child is not in pain. The author recommends further research to study pain expression in individuals with ASD.

3.3.1   Device Characteristics that Affect Stimulation Perception

The key device characteristics that can affect the shock perception include the following,

- Current
- Voltage
- Resistance
- Pulse Duration
- Shock Duration
- Output Frequency and Waveforms
- Electrode (size, locations, design, and material)
- Number and Frequency of Shocks Delivered

3.3.1.1   Current, Voltage, and Skin Resistance

The electrical output specifications that are often discussed with respect to shock devices are the *current* and the *voltage*,

- *Current (I)* refers to the amount of electricity (electrons or ions) flowing per second through a conductor. Current is measured in amperes or milliamperes (1 mA=1/1000 of an ampere). The amount of electric current that flows through the body determines various effects of an electric shock.

- *Voltage (V)* is the electrical force that drives an electric current between two points. The unit of measurement of voltage is the volt (V). One can draw an analogy to a waterfall, the voltage would represent the height of the waterfall, the higher it is, the more potential energy the water has by virtue

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of its distance from the bottom of the falls, and the more energy it will possess as it hits the bottom.

A primary variable for determining the perception of electric shock is the electric current which passes through the body. However, this current is dependent upon the voltage and the resistance (R) of the path it follows through two points in the body. The unit of measure for resistance is the ohm (Ω). The current, voltage, and resistance are all related through Ohm's Law, which states that the amount of current is equal to the amount of voltage divided by the resistance of the conductor (e.g., the human skin).

$$\text{Ohm's Law,} \quad I = V/R$$

More than 99% of the body's resistance to electric current flow is in the skin (Fish and Geddes, 2009). In ESDs, the electricity flows from one electrode (the cathode) to the other electrode (the anode) of the voltage/current source, and the current is dependent on the skin's resistance. The skin's *resistance* is dynamic and varies from person to person, stimulation site to stimulation site, and from time to time. The resistance of skin may vary from 1000 Ω to as high as 100,000 Ω on calloused, dry skin (Fish and Geddes, 2009 and Butterfield, 1975). Sweat, being rich in salts and minerals, is an excellent conductor of electricity, as is blood, with its similarly high content of conductive chemicals; therefore, the skin's resistance is much lower if it is wet or burnt/blistered and may drop to 1000 Ω.[19]

Mujenzinger and Walz (1932) stated that different fingers will experience different degrees of shock from similar stimuli especially if the shocks are very small; the difference tends to disappear with larger shocks.

The electrode-skin interface is a decidedly nonhomogeneous one. The surface of the skin is wrinkled and interrupted by pores, hair follicles, and sebaceous glands. Slow changes, over minutes, in skin resistance have been shown to occur over time, and it is hypothesized that this is due to the accumulation of sweat in the stratum corneum. The electrode structure, overlying the skin surface, traps the perspiration, gradually increasing the moisture content of the corneal layer which decreases resistance. (Mason and Mackay, 1976) Changes in voltage across time can also affect skin resistance, as skin resistance may decrease with the application of voltage. Measured between a button and a concentric ring electrode of the SIBIS electrical shock device, resistance was shown to be as high as 20 to 30 MΩ for dry skin. However, upon the fast application of a high voltage (i.e., a large change in voltage over time (dV/dt)),

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[19] DHHS (NIOSH) Publication No. 98-131 (http, //www.cdc.gov/niosh/docs/98-131/pdfs/98-131.pdf)

the skin resistance breaks down to a conducting value of 20kΩ to 30 kΩ. (Newman, 1984)

In summary, due to variations in skin resistance, it has been shown that at the same voltage setting, the output current may vary between individuals, from stimulation site to site, and from one treatment to the next.

It is worth noting that there are tables in various sources that depict the different current amplitudes that produce sensations of feeling, tingling, pain, and muscle contraction in the body (Butterfield, 1975; Nave & Nave, 1985; Fish and Geddes, 2009); however, these threshold values are more relevant under circumstances in which a body part comes into direct contact with a 60 Hz AC electrical source that pass though the chest than they are for devices, like ESDs for aversive conditioning, that provide localized stimulation to the body through electrode interfaces. The tables oversimplify the issue in this case, because they do not reflect the other factors, as discussed in 3.3 that go into determining an individual's perception of an electrical shock stimulus.

3.3.1.2 Pulse Duration

An electric current with sufficient strength and duration applied through an electrode placed on the skin will excite sensory nerves underneath the electrodes and cause a sensation that is felt by the patient. *Pulse duration* (often referred to as pulse width) is also a factor that affects a patient's sensation of an electrical shock. In normal subjects, longer pulse durations at a specific output intensity will cause an increase in the intensity and/or unpleasantness of the sensation (Ekman et al, 1966; Mason and Mackay, 1976; Newman, 1984). It has been shown that nerve excitation depends on an inverse relationship between intensity of the current and the pulse duration. Curves called "strength-duration curves" have been developed for specific nerve types and depict the minimum current necessary to excite a specific nerve, given specific pulse duration. The minimum current necessary to elicit a nerve response (e.g., a feeling of paresthesia), at a given pulse width, from a given excitable tissue is called the rheobase current. Owing to small fluctuations of excitability, a nerve fiber may not always fire if the stimulus is only slightly above the rheobase. For electrical stimulation devices designed to treat pain, it is generally thought that the stimulus should be at least twice the rheobase current amplitude (the chronaxie) for effective paresthesia to occur.
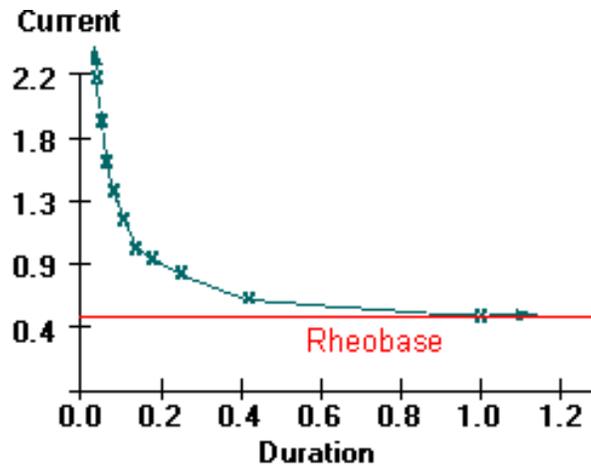
Figure 3: An Example of a Strength-Duration Curve - The Rheobase is the minimum current necessary to elicit a nerve response (e.g., a feeling of paresthesia), at a given pulse width

3.3.1.3   Shock Duration

Shock duration is the amount of time the electrical stimulus is delivered to the body.   In an article by Newman (1984), it was stated that they performed a series of experiments and found that the subjective intensity of pain from shock was a function of shock duration. However, no specific detail was provided regarding these experiments or the shock durations that were studied.

3.3.1.4   Output Frequency and Waveforms

The *frequency* of the output stimulus can also affect the perception of the electrical stimuli. When the direction of current flow (polarity) of a wave form changes over time, it is called an alternating current (AC).   The frequency of an AC signal is determined by noting the number of times the wave form changes polarity each second. The unit for AC frequencies is hertz (Hz), where one Hz is one cycle per second. Membranes of excitable tissues (e.g., nerve and muscle cells) will pass current into cells most effectively when an applied voltage is changing. The skin is somewhat similar in that it passes more current when the voltage is changing. Therefore, with AC, there is a continuous changing of the voltage and, if the current level is high enough, there will be a feeling of electric shock as long as contact is made. A direct current (DC) waveform does not change polarity, but does vary from zero voltage or current to some maximum, and this variability is the pulse rate per second or pulse frequency. For DC outputs which are pulsed, the frequency is usually given in pulses per second (pps). Direct currents increase the potential for burns. All of the FDA cleared ESDs for aversive conditioning are AC.

Studies have been conducted to delineate the relationship between the stimulation frequency and shock perception. Mason and Mackay (1976) showed that in normal subjects, a lower frequency can cause an increase in the intensity and/or unpleasantness sensation (Mason and Mackay, 1976). Mujenzinger and Walz (1932) state that at the same output current, as frequency

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increases to about 20 Hz, the perception of pain decreases. Butterfield (1975) reported on studies showing that from about 10 to 50 Hz, the frequency does not have much effect on perceived sensations. But, he reports that as you increase the frequency to above 50 Hz, sensation thresholds will increase (i.e., a higher level of current is needed to produce sensations (Butterfield, 1975).

3.3.1.5   Electrodes

The electric shock is applied to the skin of a patient using electrodes. The current travels a path between the two electrodes, referred to as the cathode (i.e., the negative terminal) and anode (i.e., the positive terminal). The size, type, and location of these electrodes can have a significant effect on perceived pain.

Size
Current Density is the amount of current flowing through a given cross-sectional area in a given time interval. It is usually measured in milliamperes per square centimeter (mA/cm^2). Thus, the size of the electrode will affect the amount of current that passes into the skin. The same current passed through a smaller electrode will elicit a stronger sensation than that same current passed through a larger electrode. For example, a 1 mA current flowing through an electrode with an area of 1 cm^2 may not be painful, but that same current flowing through a needle whose point is touching the skin is more likely to be painful. Similarly, the smaller the electrode area a given current passes through, the greater the heating effect of the current which leads to the potential for adverse events (e.g., skin burns).

Several studies have been conducted to determine the effect of varying the absolute and relative sizes of electrodes (Tursky, 1975). It was found that the smaller the electrode, the less current was needed to produce a given subjective intensity, and when there was a considerable difference in the relative sizes of the two electrodes, the sensation was felt primarily under the smaller electrode. These studies indicated that the size and the configuration of the electrodes are very important variables.

Verhoeven and van Dijk (2006), studying neuromuscular electrical stimulation devices studied electrodes placed on patella or the popliteal fossa in normal subjects. They demonstrated that, although there was individual variability in specific pain responses, when a specified output current was applied to both larger and smaller electrodes, subjects always reported reduced pain at the larger electrode. The nature of the pain was also found to differ between electrode sizes. At the smaller electrodes, pain was described as, "sharp, cutting, and lacerating" while at the large electrodes pain was described as "pinching, pressing, and gnawing."

Types
Typically, two types of electrodes have been used in ESDs for aversive conditioning. These include button electrodes and concentric ring electrodes.

The button electrode is simply a small circular electrode made of metal (e.g., stainless steel), and two electrodes are generally placed less than 6 inches apart. One electrode serves as an anode and the other as a cathode, and the current flows between them. A concentric ring electrode consists of a central button electrode surrounded by an outer ring electrode, with a few millimeters between the outer edge of the button electrode and the inner edge of the ring electrode. The two electrodes are separated using a non-conductive material. Electrode gels, which decrease the resistance between the electrode and the skin, are not generally used with these devices.

Location
The sensitivity to electrical stimuli may be increased in certain parts of the body due to the density of sensory nerves in those locations. For example, the hands, feet, genitals, underarms, torso, neck and face may be particularly sensitive to electrical stimulation.

3.3.1.6   Repeated Shocks

The *frequency of providing shocks* (i.e., providing multiple shocks within a period of time) also can affect perception of the electrical stimuli. Based on data from the use of electrical stimulation devices used to treat pain (e.g., transcutaneous electrical nerve stimulators), one may presume that habituation or adaptation would occur and that pain sensation would decrease with repeated shocks. However, this may not be true with ESDs for aversive condition, as it has been reported in normal subjects that increasing the number shocks applied causes increasing pain with each shock (Blumenthal et al., 2001; Duker et al., 1999; and Tursky, 1973). This may be due to changes in skin resistance over repeated shocks (Tursky, 1973). Blumenthal and his colleagues hypothesized that this may be due to depletion of endorphins with repeated presentation of painful stimuli. The authors also note that the fact that participants attended to the painful stimulus (in order to rate their pain) also may have contributed to the increased painfulness of those stimuli across trials (Arntz et al., 1991).

3.3.2   Individual Patient Variability

Individual body chemistry and other factors can have a significant impact on how electric current affects an individual. Some people are highly sensitive to current, experiencing involuntary muscle contraction with shocks from static electricity. Others can draw large sparks from discharging static electricity and hardly perceive it, much less experience a muscle spasm. As stated previously, it has been demonstrated in normal subjects that there is a large range of inter-subject variability with respect to the perception of equally applied shocks (Arntz and DeJongand, 1993; Blumenthal et al., 2001; Butterfield, 197; Delitto et al, 1992; Duker et al., 1990; Jones et al., 1982; and Rollmann & Harris, 1987).

Blumenthal et al. (2001) did a study in which they provided shocks to the biceps of 29 undergraduate students. The mean perceptual threshold (the level at which the stimulus was perceived) was 17.9 V, with a range between 6 and 52 V. Likewise, the

mean pain threshold (the level at which the stimulus was described as painful) was 120.9 V with a range between 48 and 200 V. Additionally, they noted that for two subjects the maximum study output of 200V was not enough to illicit pain.

Butterfield, 1975 conducted a study in which a 60 Hz shock was provided to the forearm of 10 normal subjects. The mean uncomfortable threshold was 5.3 mA with a range between 1.6 and 10 mA; the mean pain threshold was 7.6 mA with a range between 3.9 and 11.6 mA; and the mean tolerance (level above which the subject could not tolerate the stimulus) was 9.4 mA with a range of 5.1 mA to 14.1 mA. Rollman and Harris (1987) provided shocks to the forearms of 40 undergraduate students. The range of perceptual thresholds was between 0.15 and 1.43 mA; the range of pain thresholds was between 0.45 and 2.4 mA; and the range of tolerance was between 1.35 to 7.35 mA.

In addition to showing inter-subject variability between subjects, these studies also demonstrate the difficulties in comparing device outputs used to elicit pain between devices, because the articles lack many of the necessary device characteristics (discussed above) needed to make such comparisons. For example, the pain threshold in the Butterfield (1975) study was between 3.9 and 11.6 mA, while it was between 0.45 and 2.4 mA in the Rollman and Harris (1987) study. The difference may be due to differences in other device characteristics such as electrodes sizes (current densities), electrode locations, other device output parameters (e.g., pulse width and frequency), and individual subject differences.

3.3.3   Other Factors that Affect Stimulation Perception

Although there is little data available regarding the individual patient characteristics that can affect pain caused by electrical shocks, a cursory review of the literature shows that anxiety, attention, behavioral characteristics, and personality types may all be factors contributing to individual differences in shock perception.

3.3.3.1   Anxiety and Attention

The influence of anxiety on the human experience of pain and on other pain responses is still largely unclear; and the nature of the hypothesized mechanism varies widely in that some formulations imply that anxiety increases pain, while others imply that anxiety decreases pain. Arntz and DeJong (1993) reviewed 10 literature studies that have looked at the effects of experimentally induced anxiety on pain (not necessarily painful shock). Three studies showed that pain-sensitivity increased with anxiety; three studies showed there were no clear effects; four studies showed that pain decreases with anxiety.

In a study of 24 spider-phobics who received shocks under various levels of anxiety, Arntz and DeJong (1993) demonstrated that pain was rated lower when the subject's attention was diverted away compared to when the subject attended to the pain stimulus, regardless of level of anxiety. Thus, they concluded that there attentional focus rather than anxiety *per se* seems to influence pain. They hypothesize that the widely varying influences of anxiety

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on pain as observed in previous experiments and in clinical observations can be explained by considering attentional factors, but that it is conceivable that anxiety should surpass a threshold before it influences pain. Therefore, they state that dose-effect investigations, which document the effects of different levels of anxiety on different levels of pain, are needed. Delitto et al. (1992) found, in a study of 30 normal subjects, that whether the subject paid attention to the stimuli intensity versus the unpleasantness affected how they perceived the pain associated with the stimuli.

In a study of 60 normal subjects with shocks applied to the forearm, Duker et al. (1999) found no differences between focusing attention and distraction. However, they note that they used a very high current output (40 mA) in their study, and this may have affected the results in comparison to studies using much lower outputs.

3.3.3.2 Behavior Characteristics and Personality Traits

As stated previously, the subjective impressions induced by electrical stimulation can give a cutaneous sensation of intensity (e.g., touch, prick, itch, or sharp pain) as well as an emotional feeling of discomfort or unpleasantness (Delitto et al, 1992 and Tashiro and Higashiyama, 1981). In a study of 30 normal subjects exposed to neuromuscular electrical stimulation to the quadriceps femoris muscles, Delitto et al. (1992) found that preferred coping styles (monitors verse blunters) affected how subjects characterize the discomfort associated with stimuli (i.e., whether the subject primarily judged the intensity or the unpleasantness). Blunters found the applied electrical stimuli to be predominantly intense, whereas monitors found the same stimuli to be predominantly unpleasant. Duker and his colleagues (1999) found that the personality factors introversion/extroversion accounted for statistically significant differences in pain sensation ratings of clinical electric shocks, with extroverts producing lower pain scores.

3.3.4 Conclusions

A primary variable for determining the perception of electric shock is the electric current that passes through the body ,which depends upon the voltage and the resistance of the path the current follows through two points in the body. Other variables that also affect the perception of an electric shock are, pulse duration, shock duration, output frequency, waveform, electrodes (size, locations, design, and material), the number and frequency of the shocks delivered, and intersubject variability. However, this important device descriptive information is often lacking in publications on electric shock devices (Butterfield, 1975) which makes it difficult to compare the effects on pain perception of EDSs across devices.

4 Clinical Background Information regarding SIB and Aggressive Behavior

This section discusses clinical background on SIB and Aggressive Behavior and associated treatment approaches. Individuals with autism spectrum disorders, intellectual impairment, and various developmental disabilities may pose a number of behavioral challenges to siblings, parents, teachers, various therapists (e.g., occupational, physical), and their peers. Most notable is the relatively high prevalence of self-injurious behavior (SIB) that is characteristic of patients with these disorders. However, aggressive behavior is a common comorbid behavior in individuals with SIB, particularly those individuals with limited intellectual ability and/or various developmental disabilities, including but not limited to mental retardation and autism spectrum disorders. The majority of published studies on SIB typically include aggression as part of the description of the clinical spectrum or as inclusion study in a clinical study.

4.1 SIB and Aggressive Behavior in Persons with Intellectual and Developmental Disabilities

There are two major categories of destructive behavior, self-injurious behavior (SIB), and aggression toward others or toward property. The most common forms of SIB include, head-banging, hand-biting, excessive scratching and picking of the skin. The most extreme cases involve those persons with serious SIB, which is estimated to be greater than 25,000 individuals in the United States (Ross-Collins and Cornish, 2002). These behaviors involve repeated, self-inflicted, non-accidental injuries producing bleeding, protruding and broken bones, and other permanent tissue damage; eye gouging or poking leading to blindness; and swallowing dangerous substances or physical objects. SIB is especially perplexing, because to observers the repeated self-infliction of pain appears quite maladaptive and incomprehensible.

Patients with SIB frequently demonstrate aggressive behavior, which encompasses a wide range of behaviors and is generally defined as conduct that, due to its intensity and/or frequency, presents an imminent danger to the person who exhibits the behavior, to other people, or to property. Accordingly, intervention is necessary for the safety of the individual engaging in the destructive behavior, for those against whom the aggression is directed, and for the protection of property.

Less serious for the individual, but potentially more dangerous for caregivers and family, are destructive behaviors involving repeated physical assaults that injure others.

The treatment of all types of destructive behavior is difficult. In the context of concerns regarding personal freedom and dignity, many specific therapies have employed unusual, unique, and controversial approaches. Methods that employ physical or social restriction, aversive procedures, and psychotropic drugs are controversial largely because evidence of safety and effectiveness has not been rigorously studied. Relatively few studies investigating treatments for SIB and aggressive behavior are rigorous, controlled clinical trials and the majority of treatment studies typically involve single case reports and/or very small sample sizes. The methodological limitations of most studies contribute to lack of data on the safety and effectiveness of treatments for SIB and aggressive behavior.

A number of conditions/disabilities are associated with SIB and aggressive behavior and include:

- Autistic Spectrum Disorders (ASD)
- Cornelia de Lange syndrome
- Fragile X syndrome
- Hereditary sensory neuropathy
- Lesch-Nyhan syndrome
- Rett syndrome
- Severe and profound mental retardation
- Tourette syndrome
- Visual impairment

SIB and aggressive behavior are major problems in persons with developmental disabilities. According to Public Law 100-146 (10/1/87), the term developmental disability is defined as a severe, chronic disability of a person which:

A. Is attributable to a mental or physical impairment or combination of mental and physical impairments;
B. Is manifested before the person attains age twenty-two;
C. Is likely to continue indefinitely;
D. Results in substantial functional limitations in three or more of the following areas of major life activity,

1. Self-care
2. Receptive and expressive language
3. Learning
4. Mobility
5. Self-direction
6. Capacity for independent living
7. Economic self-sufficiency

E. Reflects the person's need for a combination and sequence of special, interdisciplinary, or generic care, treatment, or other services which are of lifelong or extended duration and are individually planned and coordinated.

SIB in persons with intellectual and developmental disabilities are considered to be distinct from the recently proposed Non-suicidal Self-Injury in the Diagnostic and Statistical Manual – Fifth Edition (DMS-V), as these behaviors are better explained by autism spectrum disorder and/or intellectual disability.

Estimates of the prevalence of SIB in individuals with intellectual impairment and developmental disabilities range from 2.6% to 40% (Griffin, et al 1987). More recently, MacLean et al (2010) found a prevalence of SIB of 32% in a clinic sample of children with developmental disabilities. SIB is one of the most striking and devastating conditions associated with intellectual and developmental disabilities (Cooper et al, 2009). Beyond the

obvious physical injury, self-injurious behavior can be very distressing for parents and caregivers (Hasting, 2002), severely limit a person's participation in community activities and lead to placement in a more restrictive living situation (Emerson, 2001). Once manifest, SIB is likely to continue over the lifespan, is resistant to treatment, and is costly (Emerson et al, 2001).

For adults with intellectual and developmental disabilities, considerable effort has been directed to determining risk factors for SIB and aggressive behavior. A meta-analysis study found that individuals with severe/profound intellectual and developmental disabilities, a diagnosis of autism, and deficits in receptive and expressive communication are more likely to show self-injurious behavior (McClintock et al, 2003). Similarly, visual impairment, impaired hearing, impaired mobility, and the presence of seizures have also been associated with self-injurious behavior. Although gender was not a risk factor in a meta-analysis, female gender was identified as a significant risk factor in one study (Deb et al, 2001). Adults with self-injurious behavior are also more likely to exhibit other challenging behaviors such as physical aggression, property destruction, and stereotyped behavior (Matson et al, 2008).

Studies of self-injurious behavior in older children and adolescents suggest that those with severe/profound intellectual and developmental disabilities are most likely to exhibit self-injurious behavior (Ando and Yoshimura, 1978; Chadwick et al., 2000; and Hyman et al., 1990). Lower daily living skills, impaired ambulation, visual sensory impairment, autism, and particular genetic causes (Deb, 1998) have been associated with self-injurious behavior.

4.2 Etiology of SIB and Aggressive Behavior

The etiology of SIB and aggressive behavior in persons with developmental disabilities, mental retardation and autism spectrum disorders remains unclear. Several biological and behavioral antecedents of these disorders have been suggested in the literature.

4.2.1 Biological

4.2.1.1 Biochemical

Some researchers have suggested that the levels of certain neurotransmitters are associated with self-injurious behavior. Beta-endorphins are endogenous opiate-like substances in the brain, and self-injury may increase the production and/or the release of endorphins. As a result, the individual experiences an anesthesia-like effect and, ostensibly, does not feel any pain while engaging in the behavior (Sandman et al., 1983). Furthermore, the release of endorphins may provide the individual with a euphoric-like feeling. Support for this explanation comes from studies in which drugs that block the binding at opiate receptor sites (e.g., naltrexone and naloxone) can successfully reduce self-injury (Herman et al., 1989). Research on laboratory animals as well as research on administering drugs to human subjects has indicated that low levels of serotonin or high levels of dopamine are associated with self-injury (DiChiara et al., 1971 and Mueller & Nyhan, 1982). In a study on a heterogeneous population of mentally retarded individuals, Greenberg and Coleman (1976) administered drugs, such as reserpine and chlorpromazine, presumably affect neurotransmitter regulation.

These researchers observed a dramatic increase in both aggressive and self-aggressive behavior. Drugs that elevate dopamine levels, such as amphetamines and apomorphine, also have been shown to initiate self-injurious behavior (Mueller & Nyhan, 1982; Mueller et al., 1982). FDA's literature search did not identify more recent articles on biochemical theories most likely due to the type of study needed to verify biochemical etiologies.

4.2.1.2   Seizures

Self-injurious behavior has also been associated with seizure activity in the frontal and temporal lobes. Behaviors often associated with seizure activity include, head-banging, slapping ears and/or head, hand-biting, chin hitting, scratching face or arms, and, in some cases, knee-to-face contact. Since this behavior is involuntary, some of these individuals seek some form of self-restraint (e.g., having their arms tied down). Seizures may begin, or are more noticeable, when the child reaches puberty, possibly due to hormonal changes in the body (Gedye, 1989; Gedye, 1992).

4.2.1.3   Genetic

Self-injurious behavior is also common among several genetic disorders, including Lesch-Nyhan Syndrome, Fragile X Syndrome, and Cornelia de Lange Syndrome. Patients with Fragile X or Down syndrome tend to display a higher prevalence of self-injury than that within the high-risk group of those with autism spectrum disorder (Richards et al, 2012). Since these genetic disorders are associated with some form of structural damage and/or biochemical dysfunction, these abnormalities may contribute to self-injurious behavior.

4.2.1.4   Arousal Level

A person's level of arousal may be associated with self-injurious behavior. Researchers have suggested that self-injury may increase or decrease one's arousal level. The under-arousal theory states that some individuals function at a low level of arousal and engage in self-injury to increase their arousal level (Edelson, 1984; Baumeister & Rollings, 1976). In this case, self-injury would be considered an extreme form of self-stimulation. In contrast, the over-arousal theory states that some individuals function at a very high level of arousal (e.g., tension, anxiety) and engage in self-injury to reduce their arousal level. That is, the behavior may act as a release of tension and/or anxiety. High arousal levels may be a result of an internal, physiological dysfunction and/or may be triggered by a very stimulating environment. A reduction in arousal may be positively reinforcing, and thus, the client may engage in self-injury more often when encountering arousal-producing stimuli (Romanczyk, 1986).

4.2.1.5   Pain

Individuals with various developmental disabilities and/or limited intellectual ability may engage in various SIB and aggressive behavior to reduce pain such as pain from a middle ear infection or a migraine headache (de Lissovoy, 1963;

Gualtieri, 1989). There is growing evidence that pain associated with gastrointestinal problems, such as acid reflux and gas, may be associated with self-injury. In addition, some autistic individuals report that certain sounds, such as a baby crying or a vacuum cleaner, can cause pain. In all of these instances, self-injury may release beta-endorphins which would dampen the pain. Conversely, these individuals may be "gating" the pain. In this case, stimulating one area of the body (in this case by injuring oneself) may reduce or dampen the pain located in another area of the body (Edelson, 2014).

4.2.1.6   Sensory

Excessive self-rubbing or scratching may be an extreme form of self-stimulation. The person may not feel normal levels of physical stimulation; and as a result, he/she damages the skin in order to receive stimulation or increase arousal (Edelson, 1984).

4.2.2   Behavioral

Behavioral etiologies of SIB and aggressive behavior suggest that these behaviors may be learned via operant behavior principles and maintained by positive social reinforcement, but may also be motivated by negative reinforcement, in which behavior is maintained or strengthened by the removal of an aversive stimulus. Finally, self-injury may be reinforced by sensory stimulation (Weiss, 2002). According to Weiss (2002), the more common behavioral etiologies of SIB and aggressive behavior include,

4.2.2.1   Environmental Contingencies

This concept suggests that SIB and aggressive behavior is shaped by a variety of environmental contingencies such as the need to escape a stressful situation which may explain how problem behaviors are maintained. A functional analysis of behavior can identify the relationship between environmental events and behavior, and can thus accumulate information to describe the nature of the self-injury.

4.2.2.2   Positive Reinforcement Hypothesis

The positive reinforcement explanation can be delineated into two broad classes of reinforcers, attention and increased access to desirables (Mace et al., 1994).

Attention refers to social consequences of displaying self-injury, ranging from mild to severe reprimands (i.e., social disapproval), and from sympathetic concern to physical consolation. When self-injury results in increased attention, it is positively reinforced by serving to produce social interactions that may seldom occur otherwise for some individuals with developmental disabilities, given their limited adaptive behaviors and communicative repertoires (Cox & Schopler, 1993; Mace et al., 1994; Picker, Poling & Parker, 1979).

Increased access to desirables refers to self-injury used to obtain desired tangibles or activities. It has been hypothesized that unresponsive environments and an inability to communicate requests appropriately may promote increasingly problematic behaviors (Carr & Durand, 1985). For instance, an individual may request something, not receive it, and then engage in self-injurious behavior. Additionally, the behavior may be reinforced positively if the individual should, on occasion, receive the desired object or event. A survey by Maisto et al. (1978) reported that 33% of the clients engaged in self-injury because they wanted something.

4.2.2.3   Negative Reinforcement Hypothesis

According to the negative reinforcement hypothesis, SIB/aggressive behavior is used as either escape or avoidance responses which are maintained by the delay, removal, or attenuation of an aversive stimulus (Iwata, 1987). A consistent finding in the literature has been that the highest rates of SIB are displayed during the most difficult task conditions (Carr, Newsom & Binkoff, 1980; Mace, Bowder & Lin, 1987; and Weeks & Gaylord-Ross, 1981). Some individuals engage in self-injury to avoid or escape an "aversive" social encounter (Edelson et al., 1983). The individual may engage in self-injury just prior to the social interaction; and thus, he/she may avoid the social interaction before it begins. Alternatively, the individual may engage in self-injury to escape (or terminate) a social encounter that has already begun. For example, a caretaker may ask a client to do something (e.g., to leave the play area), and if the person does not want to comply, he or she may then engage in self-injury. As a consequence, the caretaker's initial request is dropped or forgotten, and the caretaker's attention is then directed at stopping the behavior.

4.2.2.4   Self-stimulation Hypothesis

The self-stimulation hypothesis is often proposed to account for SIB that seems to occur without observable environmental contingencies (Mace et al., 1994). In this case self-injury is interpreted as providing self-induced stimulation of the senses, and develops into both sensory and social reinforcement (Edelson, 1984). For individuals with mental retardation, SIB may be more common in environments (often institutions) with insufficient stimulation. Furthermore, anecdotal reports, case studies, and neuropsychological models have suggested that individuals with autism are characterized by a dysfunctional modulation of the sensory modalities, resulting in either hypo- or hypersensitivity to stimulation (O'Neill & Jones, 1997 and Ornitz & Ritvo, 1976). Self-injury as a form of self-stimulation coincides with the idea that repetitive, stereotyped movements (e.g., body-rocking, hand-flapping) provide under-aroused individuals with stimulation (Maisto et al., 1978). In direct contrast, self-injury has also been suggested to attenuate the effects of over-arousing stimuli (Murphy, 1982).

4.2.2.5 Communication

Communication problems have often been associated with self-injurious behavior. If a person has poor receptive and/or poor expressive language skills, then this may lead to frustration and escalate into self-injury notably when the individual is trying to obtain desirable tangibles or activities.

4.3 Assessment of SIB and Aggressive Behavior in Individuals with Developmental Disabilities

The following sections provide an overview of how SIB and aggression are assessed in individuals with developmental disabilities.

4.3.1 Functional Analysis

Given that the foremost approach for treating SIB and aggressive behavior in individuals with limited intellectual and/or developmental disabilities is behaviorally based, a method known as function analysis has emerged as an effective technique for identifying unwanted or undesirable behaviors. Functional assessments allow for the identification of the relationships between SIB and relevant antecedents and consequences on an individual basis (Iwata, Dorsey, Slifer, Bauman, & Richman 1982/1994; Iwata et al., 1994; Harding et al., 2001). Functional analysis is conducted in order to obtain a detailed description of the person's self-injurious behavior and to determine possible relationships between the behavior and the individual's physical and social environment (Wacker, Northup & Lambert, 1997). Information obtained from a functional analysis typically includes,

- Identifying the individual(s) who are present during the occurrence of SIB and aggressive behavior.
- Charting events that happened before, during and after the behavior.
- Timing of the behavior.
- Location of the behavior.

Prior to data collection, it is important to define the behavior of interest. The focus of the functional analysis should be on a specific behavior (e.g., wrist-biting) rather than a behavior category (e.g., self-injury). Combining several types of self-injury into one general behavior may make it difficult to determine different reasons for each behavior. For example, if a child engages in wrist-biting and excessive self-scratching, there may be a different reason for each behavior (Edelson, Taubman, and Lovaas, 1983). Wrist-biting may be a reaction to frustration, whereas excessive scratching may be a means of self-stimulation.

During data collection, salient characteristics of the self-injurious behavior are recorded, such as the frequency, duration, and severity. In addition, data collection should also include information about the person's physical and social environment. Specifically, information regarding the physical environment should include the setting (e.g., classroom, cafeteria, playground), lighting (natural light, florescent,

incandescent), and sounds (e.g., lawn mower, another child screaming). The names (or codes) of everyone in the person's environment should also be recorded, such as teachers, parents, staff, visitors and students/clients. Other factors to be recorded include time of day and day of the week when the behaviors occur.

4.3.2 Descriptive Analysis

Descriptive analysis refers to the observation of target behaviors (e.g., SIB or aggression) in the natural environment. The direct observation of target behaviors, their antecedents, and their consequences is a hallmark of functional assessment (Gresham et al, 2001). The descriptive analysis of aggression, SIB, and other maladaptive behaviors can include many methods of collection and presentation, such as frequency counts, partial interval recording (Pace et al, 1986), and scatter plot analysis (Touchette et al, 1985).

Another commonly used form of descriptive analysis is antecedent-behavior-consequence (ABC) observations. ABC observations serve this purpose by collecting data regarding the frequency of the target behavior and information about the behavior's antecedents and consequences. Parents, teachers, and residential staff can conduct these observations using simple ABC checklists. Once this information is collected, an examiner is able to determine how many times a target behavior was preceded by a specific antecedent (e.g., an instructional demand) or followed by a specific consequence (e.g., access to a preferred item). These results then are summarized as probabilities or percentages of behavior occurring under certain antecedents and consequence conditions (Feldman and Griffiths, 1997).

4.3.3 Behavioral Rating scales

Several rating scales have been developed for the functional assessment of SIB and other maladaptive behaviors in individuals who have developmental disabilities. Two of the rating scales that have been thoroughly studied are the Motivation Assessment Scale (MAS) (Durand and Cummings, 1992) and the Questions About Behavior Functions (QABF) (Matson and Vollmer, 1995). Typically these scales are completed by the patient's primary caregiver and, in some instances, by teachers and other school personnel (e.g., school psychologists, counselors, etc.). Scales have also been developed specifically for children under the age of three years. Scales with proven psychometric properties include, Baby and Infant Screen for Children with Autism Traits, Part 3 (BISCUIT-3; Matson et al., 2009), Parental Concerns Questionnaire (PCQ; Mayo-Ortega et al., 2012), Aberrant Behavior Checklist (ABC) (Aman & Singh, 1986; Aman, Singh, Stewart, & Field, 1985a, 1985b), Behavior Problems Inventory (BPI-01; Rojahn et al., 2001, 2012a, 2012b), Repetitive Behavior Scale – Revised (RBS-R; Bodfish, Symons, Parker, & Lewis, 2000; Boyd, McDonough, & Bodfish, 2012).

4.4 Treatment of SIB and Aggressive Behavior

4.4.1 Pharmacological

There remains debate in the scientific literature with respect to both the effectiveness of pharmacological treatment of SIB and aggressive behavior and when medication management should be considered. Although several drugs have been used to treat SIB and aggressive behavior, there are only two pharmacological treatments approved by FDA for autism spectrum disorders. Risperidone was the first drug approved in 2006 to treat behaviors associated with autism in children. These behaviors were included under the general heading of irritability, and include aggression, deliberate self-injury, and temper tantrums. In 2009, aripiprazole was approved for the treatment of irritability and aggression in children ages 6–17 years of age with autism. The approval was based on data from two 8-week, randomized, placebo-controlled multicenter studies that evaluated the efficacy of oral aripiprazole for improving mean scores on the caregiver-rated Irritability subscale of the Aberrant Behavior Checklist (ABC-I). The ABC-I measures irritability symptoms associated with autistic disorder, such as aggression toward others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

Overall, the use of pharmacological treatment for SIB and aggressive behavior is reported to be generally effective although the specific rates of reduction in SIB and aggressive behavior following a pharmacological intervention are quite variable largely due to the methodological limitations of the reported studies. Nonetheless, there is reasonable consensus in the literature that the use of psychotropic drugs may help treat, or at least maintain, decreased rates of SIB in autism in conjunction with behavioral interventions, especially for those individuals for whom the function of SIB is determined to be automatic or sensory in nature. Research on psychotropic drugs has shown that the pharmacological treatments are more effective if they are based upon a putative biological mechanism underlying the SIB (Mahatmya et al, 2008). For example, SIB may be a result of dysfunctional serotonergic pathways, notably a malfunction of serotonin reuptake (Carmianti et al, 2006). Thus, the use of selective serotonin reuptake inhibitors (SSRI's) may exert their efficacy by increasing serotonin reuptake.

A recent Cochrane review (Rana et al, 2013) examined the effectiveness of pharmacological interventions in the management of self-injurious behavior in adults with intellectual disability. The Cochrane review included only randomized, placebo-controlled trials which were completed in predominantly adult populations with intellectual disabilities. From this review, several different classes of pharmacological medications have been reported to be effective in reducing/ameliorating SIB/aggressive behaviors, as described below.

4.4.1.1 Antipsychotic Agents

The Cochrane report (2013) did not include any antipsychotic trials, as these studies failed to meet their inclusion criteria (e.g., randomized, placebo-controlled trial). Nonetheless, there are numerous reports of various

antipsychotic agents for the treatment of SIB and aggressive behavior. The use of antipsychotics has shifted from typical to atypical antipsychotics, primarily because of concerns about severe side effects in children. Evidence shows that atypical antipsychotics may be useful in treating certain symptoms associated with autism spectrum disorders, such as aggression, irritability, and self-injurious behavior (McDougle et al, 2008).

The largest number of studies of atypical antipsychotic agents has been reported for risperidone. Sharma and Shaw (2012) conducted a meta-analysis of the effectiveness of reducing maladaptive behaviors in autism. The database for the analyses comprised 22 studies including 16 open-label and six placebo-controlled studies. Based on the quality, sample size, and design of studies prior to 2000, the database was restricted to articles published after the year 2000. This study aimed to examine the efficacy of risperidone treatment in ASDs. Based on the results of the meta-analysis, the overall combined effect size and sample weighted effect size fell within the large effect size range based on Cohen's classification (Cohen, 1992). The results of this meta-analysis suggest that risperidone may significantly improve many of the behavioral symptoms associated with ASD, including SIB and aggressive behavior. Overall, these results suggest that despite the various outcome measures utilized in these studies, there appears to be improvement in problematic behaviors with risperidone treatment.

Additional placebo-controlled studies also support the short-term efficacy of low-dose risperidone in adolescents with a sub-average intellectual function and various disruptive behaviors, including aggression (Pringsheim and Gorman, 2012).

Finally, other less rigorous trials of risperidone have consistently shown improvements in aggression, irritability, self-injurious behavior, temper tantrums, and mood swings in patients with autism spectrum disorders (Shea et al, 2006, Chavez et al, 2006). Both risperidone and olanzapine have been reported to reduce aggression in persons with intellectual disability (Amore et al, 2001).

Data for other atypical antipsychotic agents are limited, but ziprasidone and aripiprazole appear to show promising treatment options for SIB and aggressive behavior (McDougle et al, 2002). Aripiprazole is the second FDA approved option for the treatment of irritability and aggression in children ages 6–17 years of age with autism. The registration trials were done after several promising smaller trials of children with irritability in autism suggested this drug may have relatively good efficacy (Stigler et al, 2004, 2009; Valicenti-McDermott & Demb, 2006). In a study of five children given an average of 12 mg daily for 3 months, 100% of them had improvement in their aggression, self-injurious behavior and tantrums.

Olanzapine and quetiapine have shown minimal clinical benefit in autism spectrum disorders and are associated with marked weight gain and sedation (Baptista et al, 2008). A recent study by Golubchik and colleagues (2011) suggested that low-dose quetiapine may reduce aggression levels and increase sleep quality in adolescents with autism spectrum disorders.

Two case reports found clozapine, in doses of 200 to 450 mg/day, effective for reducing aggression in children and adolescents with autism (Zudda et al, 1996; Chen et al, 2001).

4.4.1.2   Antidepressant Agents

There have been several small studies that showed that selective serotonin reuptake inhibitors (SSRIs) may improve both the stereotypic and obsessive-like behavior associated with self-injury and aggression. In two Japanese studies, fluvoxamine helped reduce aggression in addition to stereotypy in children with autism (Fukuda et al., 2001; Yokoyama et al., 2002). Currently, fluoxetine, escitalopram, clomipramine, and sertraline are approved for major depressive disorder and obsessive-compulsive disorder in children (down to six years of age). These SSRIs have been found to decrease aggression in individuals with autism. Moreover, the drugs have shown dose-dependent effects on SIB, with higher doses typically more effective in reducing aggressive behavior (Carmianti et al, 2006).

Other antidepressant agents such as clomipramine and desipramine were found to be superior to placebo for the treatment of several symptoms, including SIB in children and young adults with autism (Gordon et al, 1993).

Evidence of the efficacy of older tricyclic antidepressants with the exception of desipramine, buspirone, and venlafaxine has not been reported beyond single case reports involving only one or two subjects.

4.4.1.3   Opioid Antagonists

A recent Cochrane report (Rana et al, 2013) identified four double-blind, placebo-controlled trials which compared the effects of naltrexone versus placebo. One of the naltrexone versus placebo trials reported that naltrexone had clinically significant effects (≥33% reduction) on the daily rates of three of the four participants' most severe form of SIB and modest to substantial reductions in SIB for all participants; however, this study did not report on statistical significance. Another trial reported that naltrexone attenuated SIB in all four participants, with 25 mg and 50 mg doses producing a statistically significant decrease in SIB. Another trial (N=8) reported that naltrexone administration was associated with significantly fewer days of high frequency self-injury and significantly more days with low frequency self-injury. Naltrexone had different effects depending on the form and location of self-injury. Another trial with 26 participants found that neither single-dose (100

mg) nor long-term (50 and 150 mg) naltrexone treatment had any therapeutic effect on SIB.

Other research on opioid antagonists has suggested that the treatment targets peripheral behavioral symptoms and not the core symptoms of autism; naltrexone helps decrease withdrawal and SIB, and somewhat increases verbal behavior (Elchaar et al, 2006; Willemsen-Swinkels et al, 1996). It also has dose-dependent effects, with optimal benefits observed at doses between 0.5 and 2.0 mg/kg (Campbell et al., 1993; Elchaar et al, 2006; Taylor et al, 1991). Additionally, naltrexone may be more beneficial for certain individuals with SIB and autism. The research suggests that individuals with severe and non-socially reinforced SIB are better responders to the drug; those with lower — beta-endorphin levels also tend to respond better (Elchaar et al, 2006; Taylor et al, 1991). Symons, Thompson and Rodriguez (2004) also found that males respond better than females with females often requiring extremely high doses.

However, despite these positive findings, there are some paradoxical findings in the naltrexone research. The use of naltrexone may in fact worsen SIB and aggressive behavior in the long-term, increasing relapse rates if discontinued, and in some cases naltrexone treatment was not found to be different than placebo (Benjamin et al, 1995; Campbell et al, 1993; Willemsen-Swinkels et al, 1995). In general, naltrexone is only found to be effective for severe SIB in short-term instances with much individual variation in responding.

4.4.1.4 Mood stabilizers/Anticonvulsant Agents

Mood stabilizers, namely lithium, and the anticonvulsant agents have been used to treat aggression in a variety of psychiatric disorders, including autism. Most studies have been limited to case reports. In a single patient case report, lithium was used to augment fluvoxamine in the treatment of aggression. The dose was 900 mg and lithium augmentation did lead to a significant reduction in aggression (Epperson et al., 1994).

One open-label trial of divalproex sodium to treat irritability and aggression in autism used an average dose of 768 mg/day in 14 people ages 5–40 (Hollander et al., 2001). Target symptoms encompassed impulsivity, aggression, and mood instability. The outcome was measured using the clinical global impression improvement scale (CGI-I). While 71% of subjects were much or very much improved, side effects were present including alopecia, behavioral activation, elevated liver enzymes, sedation and weight gain. A larger prospective trial in 30 autistic youths ages 6–20 examined the difference in aggression after treatment with either divalproex sodium or placebo (Hellings et al., 2005). Despite adequate blood levels, the two groups did not differ in reduction of irritability based on the ABC-I subscale.

Other anticonvulsant agents such as lamotrigine, topiramate, and levetiracetam have yielded equivocal results in reducing either SIB or aggression in persons with developmental disabilities (Robb, 2010).

4.4.1.5 Alpha Agonists

Alpha-2 adrenergic agonists, notably clonidine and guanfacine have been investigated primarily to treat irritability in children with autism. One double-blind, placebo-controlled crossover study reported an effect of transdermal clonidine in reducing self-stimulating behaviors (Frankhauser et al, 1992). A retrospective trial of guanfacine in 80 patients ages 3-18 with autism spectrum disorders failed to reduce aggression in persons with pervasive development disorder (Posey et al, 2004).

4.4.1.6 Other Pharmacological Interventions

4.4.1.6.1 Amantadine

In a double-blind, placebo-controlled 5-week trial of amantadine in 39 children, ages 5-19 with autism the active medication helped reduce symptoms of irritability and aggression in 47% of the children compared to 37% on placebo with reduced symptoms (King et al, 2001).

4.4.1.6.2 Ammonia

While not technically a prescription drug, ammonia has been used as a noxious pharmacological agent in an attempt to reduce SIB and aggressive behavior in developmentally disabled persons. There have been several case report studies investigating the use of ammonia to eliminate or reduce SIB. The earliest report of the use of ammonia to treat SIB dates back to 1975 (Tanner & Zeiler, 1975). Punishment with aromatic ammonia was used to eliminate self-injurious behavior of an autistic woman during experimental sessions. The effects were reversible but were limited to experimental sessions until staff used the ammonia on the ward at all times.

Baumeister & Baumeister (1978) described the treatment of two institutionalized children who exhibited high rates of severe SIB with aromatic ammonia inhalation on a response-contingent basis. These authors reported rapid and sustained suppression of SIB which persisted even when the ammonia inhalation treatment was discontinued.

Singh et al (1980) conducted two experiments which investigated the effects of behavioral interventions on the self-injurious behavior of two profoundly retarded girls. In the first experiment, response-contingent aromatic ammonia was used as the aversive stimulus to reduce the high frequency of face-slapping and face-hitting in a deaf

and blind girl. In the second experiment, an overcorrection procedure was used to control jaw-hitting in another girl. In both cases, the treatments resulted in near-zero levels of self-injury. However, complete suppression of self-injury was not achieved.

Rapoff et al (1980) employed a combination of multiple baseline and reversal designs to examine the effects of differential reinforcement, overcorrection, lemon juice, and aromatic ammonia on the rate of self-poking in a profoundly retarded child. Both differential reinforcement and overcorrection were ineffective. Although lemon juice suppressed and stabilized the rate of poking, aromatic ammonia produced greater suppression.

4.4.1.7 Adverse Events Associated with Pharmacological Interventions

Adverse events associated with pharmacological treatment of SIB and aggressive behavior in persons with intellectual impairment, autism spectrum disorder and various developmental disabilities are similar to those seen in other patient populations for which these medications are indicated. There is no evidence in the scientific literature that patients with intellectual and developmental dysfunction are at any greater risk of developing adverse events.

The adverse event profile of antipsychotic agents used to treat SIB and aggressive behavior appear to be similar to that reported for major psychiatric disorders (McDougle et al, 2002; Matson et al, 2008; Robb, 2010). These include sedation, weight gain, development of involuntary movements (e.g., tardive dyskinesia, dystonia. akathesia), elevated prolactin levels, cardiac conduction changes and neuroleptic malignant syndrome.

Common adverse events associated with SSRI's include headache, hyperactive behavior, gastrointestinal effects, anxiety, sexual dysfunction and mild weight gain (Mahatmya et al, 2008). Common side effects associated with tricyclic antidepressant medications include weight gain, dry mouth, sedation, and, in some instances, cardiac conduction changes.

Opioid antagonists tend to be relatively well-tolerated. In studies of naltrexone, there was one reported event of nausea and sedation; however, the patient was also taking clonidine for which sedation is a common side effect. No serious adverse events have been reported in studies using opioid agonists for SIB and aggressive behavior.

Mood stabilizers, including lithium and anticonvulsant agents, often require monitoring of cardiac function, kidney function, and routine blood tests to assess for evidence of toxicity that can be associated with several serious adverse events, including coma and death. Common, less serious adverse events associated with mood stabilizers include sedation, changes in appetite and weight, and skin rash.

The major adverse event associated with alpha agonist medications is sedation. Since these medications were developed primarily for the treatment of hypertension, studies have reported some patients who experienced non-life threatening hypotension (Robb, 2010).

4.4.2 Behavioral

The most common approach for the treatment of SIB and aggressive behavior in individuals with intellectual impairment and developmental spectrum disorders is behaviorally based. Research has demonstrated that for many individuals SIB is socially mediated and warrants environmental modifications (Iwata, Pace, et al., 1994). Determining the function of SIB and aggressive behavior and selecting treatments based on these functions is important for successful treatment. Functional assessments allow for the identification of the relations between SIB and aggressive behavior and relevant antecedents and consequences on an individual basis (Iwata, Dorsey, Slifer, Bauman, & Richman 1982/1994; Iwata et al., 1994; Harding et al., 2005). The results of functional assessments subsequently guide the process of selecting appropriate and functionally relevant behavioral interventions.

Kahng and colleagues (2002) conducted a quantitative analysis of behavioral research on the treatment of SIB which included a literature search covering the period from 1964 to 2000. This search yielded 396 articles (706 participants) on the treatment of SIB. Most research participants are male and diagnosed with severe/profound mental retardation. The mean outcome of all reported treatments was an 83.7% reduction in SIB from baseline to treatment, and most treatments were successful in reducing SIB by at least 80% using a variety of behavioral techniques. The authors concluded that the use of reinforcement-based interventions has increased during the past decade, whereas the use of punishment-based interventions has decreased less. Most treatments have been highly effective in reducing SIB; nevertheless, the disorder persists in spite of an abundance of research, suggesting that a greater emphasis should be placed on prevention.

The behavioral treatment of SIB and aggressive behavior has been extensively studied in the literature and, for the most part, is based upon the principles of operant conditioning first described by B.F. Skinner. Thus, aggression by individuals with developmental disabilities is believed to be a learned behavior or set of behaviors. The individual has learned that aggressing towards another individual achieves a desired outcome, i.e., the aggressive behavior becomes functionally related to the consequences that reliably follow it (Foxx & Meindl, 2007).

Various positive and negative reinforcement paradigms have demonstrated success in reducing or significantly eliminating a variety of self-injurious behaviors and aggression towards persons and objects. A basic tenet of

behavioral interventions for SIB and aggressive behavior is that early and effective intervention is essential in order to impact behavior change. The research synthesis by Horner et al. (2002) showed that the early use of behavioral interventions can result in reductions of challenging behaviors by 80–90%. A negative corollary is that in the absence of intervention, challenging behaviors tend to persist in individuals with developmental disabilities (Murphy et al., 2005).

There are a wide variety of behavioral interventions that have been employed for the treatment of SIB and aggressive behavior in individuals with developmental disabilities and/or limited intellectual function. Behavioral interventions essentially fall into four broad categories,

4.4.2.1 Reinforcement-Based Treatments

There are several reinforcement schedules that have empirical support for use in severe behavior problems. Traditionally, a distinction is made between *positive* reinforcement and *negative* reinforcement; however, both have the goal of eliminating an unwanted or undesirable behavior. Positive reinforcement paradigms generally reward the individual for exhibiting appropriate behaviors whereas negative reinforcement paradigms (e.g., time out, withdrawal of privileges, food, play activities, etc.) generally "punish" the individual for exhibiting an unwanted behavior or non-compliance with various requests. The term punishment is controversial in that it is often interpreted as consisting of physical punishment, when in fact there are several different types of negative reinforcement paradigms that are utilized, including time-out, withholding of desirable or tangible objects, and restraint, among others. Negative reinforcement schedules may be less useful with respect to SIB and aggressive behavior, as these behaviors are particularly susceptible to socially mediated escape and avoidance contingencies, as the severity of the behavior often requires termination of ongoing activities, such as classroom activities or other treatment programs. Thus, terminating an activity may be analogous to a time-out which results in actually reinforcing the very behavior one is trying to eliminate.

Noncontingent reinforcement (NCR) is scheduled to occur at a continuous interval without regard for whether or not individuals are engaging in appropriate behavior or SIB and aggressive behavior. Availability of NCR is not contingent on the behavior of an individual. NCR has been shown to be an effective means for reducing the frequency of severe problem behavior (Fischer, Iwata, & Mazaleski, 1997; Hanley, Piazza, & Fisher, 1997; Vollmer, Iwata, Zarcone, Smith, & Mazaleski, 1993; Wilder, Draper, Williams, & Higbee, 1997).

Other reinforcement schedules are based on the concept of differential reinforcement. That is, the appropriate behaviors an individual engages in are reinforced, and the target behaviors are ignored based on a pre-identified

schedule. In the differential reinforcement of other behaviors (DRO), individuals are reinforced for not engaging in SIB and aggressive behavior for a set period of time. DRO schedules require continuous monitoring by a therapist to determine whether the criterion for reinforcement (i.e., no responding throughout the DRO interval) has been met (Vollmer et al, 1995).

Other variations include the differential reinforcement of incompatible behaviors (DRI) and the differential reinforcement of low rates of behavior (DRL). In a DRI schedule, individuals are provided with reinforcement for engaging in a behavior that is not compatible with the target behaviors. In a DRL schedule, a predetermined acceptable rate of SIB is established and individuals receive reinforcement for engaging in a rate at or lower than that predetermined rate. In reinforcement schedules, reinforcement can come in the form of social attention, access to preferred items or activities, or a brief break from demands (Wacker et al, 1997).

4.4.2.2 Extinction-Based Treatments

Extinction is defined as no longer providing reinforcement for a response that was previously reinforced. By terminating the contingency between the response and the reinforcement, extinction procedures result in a decreased probability that the response will occur again. Extinction is a common component of many behavioral interventions and has been demonstrated to be highly effective in the treatment of SIB and other maladaptive behaviors (Thompson et al, 2003). In addition, extinction is shown to be the crucial component in the efficacy of other interventions, such as functional communication training (FCT) (Kelly et al, 2002).

SIB and aggressive behavior is often maintained by negative reinforcement in the form of escape from the environmental setting or the demands of a specific task (e.g., remaining seated in the classroom, etc.). By engaging in either SIB or aggressive behaviors, the individual is often removed from the setting which inadvertently negatively reinforces (and maintains) SIB and aggressive behavior. To eliminate or extinguish this behavior, eliminating the escape contingency has been shown to be an effective treatment (Iwata et al, 1990).

A form of extinction frequently used for severe forms of SIB that are maintained by sensory reinforcement is protective equipment. Protective equipment (e.g., helmets, face shields, and gloves) frequently is recommended for dangerous forms of SIB that could result in tissue damage or severe injury. Protective equipment, however, also is used as a method of reducing behavior maintained by sensory reinforcement (Dorsey et al, 1982). The rationale behind the use of protective equipment is that if the SIB functions to provide positive reinforcement in the form of sensory experiences, then protective equipment serves as an extinction procedure by blocking that positive reinforcement.

However, a potential "adverse event" associated with extinction procedures is the risk of so-called extinction bursts which is an upsurge, particularly in the early stages of the intervention, of the actual undesired or unwanted behavior. If this upsurge in behavior poses a danger to the individual and/or others, then an extinction paradigm is not a feasible option (Lerman et al, 1999).

4.4.2.3 Punishment-Based Treatments

Over the past decade, the consensus in the scientific literature has been that the initial behavioral intervention should be the least restrictive option available that still results in behavior reduction (Foxx, 2005). Although the first choice of behavioral interventions typically is the selection of reinforcement and extinction-based strategies, there are times when more invasive methods are necessary to gain control over dangerous behaviors, such as SIB and aggressive behavior, especially when these behaviors have the potential to cause serious injury to the self or others (Minshawi, 2008). Punishment is defined as the presentation of an aversive stimulus or the removal of a positive stimulus contingent on engaging in a target behavior, such as SIB (Kazdin, 2001).

Although the use of punishment procedures is questionable with respect to its effectiveness in the treatment of SIB and aggressive behavior, Foxx et al (2005) has argued against entirely dispensing with this form of aversive treatment. Some individuals who have developmental and/or intellectual disabilities engage in problem behaviors of sufficient severity to threaten their own lives. Eliminating the use of aversive interventions in these individuals may limit the available treatment options (Foxx et al, 2005).

The key feature of the use of punishment in behavior intervention is that the punishing stimuli (e.g., water mist) or event (e.g., time out from positive reinforcement) must be strong enough to override the maintaining reinforcement for the behavior (Iwata et al, 1990).

Several punishment methods have demonstrated some degree of effectiveness in individuals who have autism. For example, when SIB is related to reinforcement in the form of contingent attention, time out from positive reinforcement has proved moderately successful in decreasing maladaptive behaviors (Harris & Ersner-Hershfield, 1978). Another punishment procedure used in the treatment of SIB is contingent physical exercise. Contingent physical exercise consists of having individuals engage in brief physical activity immediately after an occurrence of the target behavior (Luce et al, 1980). This procedure originally was designed for use with aggressive and disruptive behaviors but recently has been applied to the treatment of SIB in individuals who have autism and intellectual impairment (Foxx & Garito, 2001).

The punishment procedure that has received the most debate is physical restraint. Physical restraint can range from complete immobilization on a bed, for example, to limiting the mobility of specific body parts (e.g., rigid arm

sleeves). Based on the limitation of movement provided by physical restraints, this option may be viewed as the most restrictive behavioral intervention. Furthermore, the application of physical restraints can make it difficult or impossible for individuals to engage in appropriate, adaptive behaviors. Despite these concerns, the programmatic use of physical restraint in severe instances of SIB has been shown effective. For example, rigid arm restraints have been used in many studies to reduce the frequency of SIB, especially hand-to-head SIB (Kahng et al, 2001; Fisher et al, 1997).

Use of restraints is not usually considered a "last resort" intervention. The goal is to fade the use of restraints gradually over time, so that individuals remain under the stimulus control of the restraints while not actually wearing them. The use of physical restraints should be conducted in a systematic manner with careful consideration being given to providing the least amount of restraint necessary to reduce harm while inhibiting adaptive behaviors as little as possible (Wallace et al, 1999).

4.4.2.4   Functional Communication Training (FCT)

FCT is a procedure in which a socially appropriate communicative behavior is taught to replace a less appropriate behavior. The operant function of the behavior such as aggression is identified, reinforcement is provided for the alternative response and the behavior is placed on extinction. The new behavior becomes a more effective means to achieve the desired outcome, thus the necessity to emit the less appropriate behavior is diminished. FCT empowers the individual to regulate the delivery of the reinforcer, thereby exerting more control over their environment. Several studies have demonstrated the effectiveness of FCT in reducing aggression especially when included as part of a comprehensive, multi-modal treatment plan (Braithwaite & Richdale, 2000; Grace et al, 2009; Thompson et al, 1998; Ringdahl et al, 2009).

4.4.3   Other Treatments

In addition to the more common behavioral and pharmacologic treatments for SIB and aggressive behavior, there have been numerous other treatments reported in the scientific literature for SIB and aggressive behavior. Most of these studies are single case reports or included a relatively small sample size. Nonetheless, the findings from these studies consistently report that the majority of these treatments have demonstrated some degree of effect in reducing SIB and aggressive behavior. Additional treatments for SIB and aggressive behavior are described below.

4.4.3.1   Surgical

Surgical treatment of aggressive behavior is not a recent concept. The earliest report dates back to the early 1960s. Initial studies focused on surgical ablation of the amygdala which has long been described as the putative anatomical structure involved in aggression. The majority of these early reports relied

primarily on parent, physician/nursing or ward staff observations of behavior to document improvement.

4.4.3.1.1 Ablative Interventions

The earliest report of the use of amygdalotomy was reported by Narabayashi et al (1963, 1966). In these studies, amygdalotomy was conducted on 60 patients, 14 of whom were under 14 years of age. These patients were described as irritable, excitable, distractible and assaultive and reported an initial response rate of 85% that was reduced to 68% at three to six years of follow-up.

Vaernet and Madsen (1970) reported 12 female patients ages 23-69 years, six of whom were diagnosed with schizophrenia that demonstrated violently aggressive behavior with assaults on fellow patients and ward personnel, and/or a marked tendency towards self-mutilation. After bilateral amygdalodotomy there was a marked improvement in or disappearance of aggressive behavior in all but one patient.

Balasubramaniam and Ramamurthi (1970) reported the results of amygdalodotomy in 100 aggressive children and adults. Unfortunately, few details of the psychiatric state pre- and postoperatively are given. The authors reported that 75 patients demonstrated either complete or almost complete cessation of aggressive behavior.

Kiloh and colleagues (1974) reported the effectiveness of amygdaloidotomy that was performed bilaterally on 15 and unilaterally on three patients exhibiting severe aggressive or self-mutilating behavior. Nine subjects (50%) were improved a year after operation; improvement was maintained in seven (39%) for periods ranging from 27 months to nearly six years. Four non-epileptic cases had convulsions during the period of review; one patient had a persistent mild hemiparesis dating from the postoperative period. There was a tendency for epileptics to respond better than non-epileptics and for mentally retarded patients to respond poorly; however, none of the differences were statistically significant.

Psychosurgery for patients with self-mutilating behavior has focused on the use of limbic leucotomy (Price et al. 2001). These authors described five patients with primary psychiatric diagnoses which included obsessive-compulsive disorder or schizoaffective disorder with co-morbid severe, treatment-refractory SIB. The primary outcome measure was the clinical global impression scale which indicated that sustained improvement was noted in four of five patients with a substantial decrease in SIB.

Psychosurgery for SIB in Tourette syndrome (TS) has also been investigated as SIB is a common co-morbid behavioral disorder in TS and is present in anywhere from 25-50% of patients (Robertson et al, 1989). Anandan and colleagues (2004) described in a case report the use of cingulotomy and subsequent limbic leucotomy in an adolescent boy with Tourette's Disorder for SIB. The patient's repetitive and medically serious SIB and failure of all other treatments prompted this intervention after careful, comprehensive review and discussion. Following the second surgery, the severity and frequency of his SIB were reduced.

More recently, Jimenez-Ponce and colleagues (2011) conducted a prospective analysis of the efficacy and safety of bilateral cingulotomy and anterior capsulotomy for aggressive behavior. This article is in Spanish; the English language abstract indicates these authors studied 25 patients with a primary diagnosis of aggressiveness refractory to conventional treatment. Subjects were clinically evaluated with the Mayo-Portland adaptability inventory and the Global Assessment of Functioning score. Based on inclusion and exclusion criteria, 12 patients were finally included and surgical treated. The surgical intervention significantly decreased aggressive behavior as assessed by the Mayo-Portland adaptability inventory and the Global Assessment of Functioning score at 3 and 6 months follow-up. Only five patients showed either mild or transitory postsurgical complications. These authors concluded that combined bilateral anterior capsulotomy and cingulotomy successfully reduced aggressiveness behavior and improved clinical evaluations. These effects were obtained with fewer complications than previously described surgical targets.

4.4.3.1.2 Brain Stimulation

There are no FDA-approved DBS devices for the treatment of SIB and aggressive behavior. The idea that deep brain stimulation (DBS) of certain neuroanatomical areas to ameliorate aggressive or SIB is largely based upon putative functional neuroanatomical targets that purport to mediate these behaviors. The earliest description of stimulation dates back to 1970 when Sano et al (1970) used a combination of stimulation and ablation procedures of the posterior hypothalamus to treat disruptive and aggressive behaviors in a series of 51 patients with pathologically aggressive behavior. The authors report a "marked calming" effect in 95% of the cases during the follow-up period which ranged from two to seven years. The results of the operation were classified as "excellent" if the patient showed no violent, aggressive, or restless behavior, was calm and placid, and required no care or supervision; and "good" if the patient showed occasional irritability, but was usually calm and tractable and required no constant watch and care. Among the 42 cases, excellent results were obtained in 12 and good results in 28 cases. No significant adverse events were noted in this report.

Franzini et al (2005) described the therapeutic effect of chronic continuous high frequency DBS of the posterior hypothalamus on two patients with aggressive and disruptive behaviors who were resistant to drug or behavioral interventions. Both patients were mentally retarded but also had other medical complications (myoclonic epilepsy, congenital toxoplasmosis). In both cases, DBS resulted in consistent improvement of disruptive behavior which remained present at a one year follow-up. The methods by which disruptive and/or aggressive behavior were assessed is not described in this study. More recently, Franzini et al (2013) summarized their experience with DBS for the treatment of aggressive and disruptive behaviors refractory to conventional pharmacological or behavioral treatment. This included a summary of seven patients who underwent bilateral DBS of the posterior hypothalamus. The lack of cooperation from all patients was attributable to the severity of both the disruptive behavior and of the most prominent comorbid condition (e.g., mental retardation). Six of the seven patients obtained a marked reduction in their aggression and disruptive episodes as assessed by the Overt Aggression Scale. The authors did not report any serious adverse events in their case series.

Kuhn and colleagues (2008) described a case report of a 22 year old female with repetitive oral self-mutilating behavior after a severe traumatic brain injury treated with bilateral DBS of the posterior hypothalamus. This procedure resulted in the complete elimination of self-mutilation during a 4-month observation period.

4.4.3.2 Physical Restraint

Physical restraint that is not utilized as a punishment technique as noted above, has been used to treat SIB and aggressive behavior. Thus, physical restraint which prevents the individual from carrying out SIB or aggression is technically not considered as punishment (Minshawi, 2008).

Restraint as applied to people with intellectual disabilities refers to any actions to limit the movement of an individual. Because restraint can be highly restrictive, poses a risk of injury, and can result in death; its use must be minimized, reduced, and eliminated if possible. Physical restraint can range from complete immobilization on a bed, for example, to limiting the mobility of specific body parts (e.g., rigid arm sleeves).

There is great variation in the type of restraint used to manage self-injury. Mechanical restraints, for example, can range in their form of restrictiveness and degree of restrictiveness, from almost complete immobilization using objects such as beds or chairs, to the use of wrist cuffs that bring the SIB under stimulus control but which do not restrict movement. Mechanical forms of restraint have received the greatest attention in the literature on self-injury, and

some epidemiological studies report on the prevalence of use. Population studies of people with intellectual disabilities and challenging behavior in one health region in the UK in the early to mid-1980s showed that approximately 1.3 percent (75 individuals) of people with intellectual disabilities who self-injured wore protective devices or mechanical restraints (Murphy et al, 1993; Oliver et al, 1987). Arm splints were the most commonly used device. These people had severe SIB, were generally younger, and had greater sensory, cognitive and physical impairments than other people with SIB. They also tended to present multiple forms of challenging behavior.

The use of physical restraint presents a higher risk of injury and the possibility of death; however exact rates of injury or death from the use of physical restraints remains unreported. Restraint usage should be one of the most important, closely managed areas of clinical practice in behavioral services. The use of restraint has a rather small risk of injury to recipients with intellectual disabilities but this risk nonetheless remains present (Williams, 2009).

4.4.3.3   Sensory Integration Training (SIT)

This technique is based upon the theory that a dysfunction in sensory processing contributes learning and behavioral challenges in individuals with disabilities (Ayres, 1972). The goal of sensory integration treatment is stimulation of neural processes involved in receiving, modulating, and integrating sensory input. As a result of such stimulation, it is hypothesized that the nervous system begins to properly process sensory stimuli, which in turn leads to an improvement in adaptive functioning and decreases in maladaptive behaviors.

A vast body of literature exists that addresses outcomes, efficacy, or effectiveness of the sensory integration approach. For example, Daems (1994) compiled reviews of 57 outcomes studies published between 1972 and 1992 that evaluated interventions based on sensory-integration theory which yielded equivocal results largely due to study design limitations. More recently, Vargas and Camilli (1998) reported a meta-analysis of 32 SIT studies across various diagnoses. The review demonstrated that well-designed rigorous studies demonstrated that SIT did not benefit individuals receiving the intervention. Despite the availability of outcome studies published over the past 30 years, evidence of the effectiveness of this intervention remains inconclusive.

One popular SIT intervention is the use of weighted vests. Weighted vests are close-fitting garments in which small weights are placed in pockets or interior slits, which provide proprioceptive and tactile stimulation to the wearer. This stimulation is intended to have multiple benefits, including a decrease in problem behavior (Stephenson & Carter, 2009). However, more recently, Davis et al (2013) have suggested that the use of weighted vests does not appear to decrease challenging behavior.

Other types of SIT have included the use of daily tactile and vestibular stimulation with relatively good success in reducing SIB and aggressive behavior (Wells & Smith, 1983).

4.4.3.4   Mindfulness Training

The mindfulness procedure is based upon the book, *Meditation on the Soles of the Feet* (Singh et al, 2003) which is a meditation technique which requires the individual to shift their awareness and attention from anger-producing situations to a neutral point on the body, i.e., the soles of the feet. These authors report a single case report of an adult with mental retardation whose aggression precluded community placement that was eliminated using this technique. The individual remained aggression-free for up to one year following readmission to a group home.   Individuals with moderate to severe levels of mental retardation appear to be less responsive to this procedure as it is difficult for individuals with more compromised intellectual function to comprehend the verbal instructions necessary for successful completion of this technique.

4.4.3.5   Contingent Exercise

Generally considered to be a form of behavioral treatment, contingent exercise or effort is a method which requires the individual to exhibit a change in behavior as a consequence of their SIB and aggressive behavior (Kazdin, 1975). One type of contingent effort that has been applied in individuals with severe emotional disturbances is so-called contingent exercise. Contingent physical exercise consists of having individuals engage in brief physical activity immediately after an occurrence of the target behavior (Luce et al, 1980). This procedure originally was designed for use with aggressive and disruptive behaviors but recently has been applied to the treatment of SIB in individuals who have autism and intellectual disabilities (Foxx and Garito, 2007; Kahng et al, 2001). Luce et al (1980) utilized contingent in two single-subject experiments. The contingent exercise, required standing up and sitting on the floor five to ten times contingent on inappropriate behavior, including aggressive actions and aggressive comments. In both experiments, aggression was consistently reduced in frequency via the use of contingent exercise. The authors concluded that contingent exercise was a more effective behavioral procedure, notably when other forms of differential reinforcement of other behaviors failed.

4.4.3.6   Muscle Relaxation

The use of progressive muscle relaxation training is a key component of behavioral treatments, notably systematic desensitization therapy which is used in a variety of psychiatric conditions, including anxiety and phobic disorders and as a stress reduction technique. The use of muscle relaxation to reduce aggressive behavior in mentally handicapped patients was first reported by Lindsay and Baty (1986) and subsequently by McPhail and Chamove (1989). Fung To and Chan (2000) reported a modest reduction (15%) of aggressive

behavior was achieved via the use of muscle relaxation and concluded that overall, the literature on the outcomes of muscle relaxation training in reducing aggressive behaviors is inconclusive particularly in individuals with limited intellectual ability and developmental disabilities presumable due to their lack of cognitive capacity to understand and carry out the procedures required for progressive muscle relaxation.

4.4.3.7   Snoezelen Room

A form of multi-modal sensory stimulation is provided in Snoezelen rooms which are multi-sensory environments that have been used to improve behavior and quality of life of individuals with mental retardation (Hogg et al, 2001). These rooms typically contain an array of multi-sensory equipment that provide stimuli in several modes, olfactory (e.g., aromatherapy diffuser and assorted scents, scented magic markers), vibratory and tactile (e.g., assorted vibrators and body massagers, somatron bean bag with vibrations synchronized to music), auditory (e.g., electronic nature sounds generator, complete stereo system), and visual (e.g., laser light show devices, rotating disco balls, interactive light panels with mirrors, interactive fiber optic fountain, fiber optic curtains). In addition, there may be a number of rockers (vestibulator swing devices with bolster swings, net swings, and tumble form sitters), beds, and mats. The floor of a Snoezelen room is carpeted, the walls are painted in various luminescent colors, and music is played softly in the background.

Singh and colleagues (2004) investigated the effects of the Snoezelen room for treating SIB and aggressive behavior in 15 adults with severe or profound mental retardation before, during and after being treated with activities of daily living training program, vocational skills training and in a Snoezelen room. Both aggression and self-injury were lowest when the individuals were in a Snoezelen room. The difference in levels before and after Snoezelen were statistically significant with self-injury but not with aggression.

4.4.3.8   Electroconvulsive Therapy (ECT)

The use of ECT in pediatric and adult patients with intellectual and developmental disabilities with SIB and aggressive behavior is an area of growing interest with multiple reports demonstrating both safety and efficacy, in reducing SIB and aggressive behavior without serious adverse events (Aziz et al, 2001; Reinblatt et al., 2004; Rey & Walter, 1997; and Wachtel et al., 2009). However, ECT has not been approved by FDA for the treatment of SIB and aggressive behavior.

Though ECT also utilizes an electrical stimulus applied to the skin, it is different from ESD for aversive conditioning in several important ways. First, the purported mechanism of action of ECT involves the initiation of seizure activity from the applied electrical stimulation. The purported mechanism of action of ESD involves aversive conditioning that is accomplished by inducing some level of pain and discomfort from the applied stimulus. ECT is

administered (in the U.S.) under general anesthesia, therefore, individuals generally do not experience pain and discomfort from the stimulation. ECT and ESD for aversive conditioning also differ in terms of the indications for use. ECT is indicated to treat depression and other psychiatric conditions; it is not indicated use to treat SIB and aggressive behavior in individuals with limited intellectual ability or those with various developmental spectrum disorders. Another distinction is that ECT typically has a defined time-limited course of treatment. ECT devices are regulated under 21 CFR § 882.5940.

More recently, Wachtel and colleagues (2011) reported the successful use of ECT in an 11-year-old boy with autism and a 4-year history of psychotropic-resistant bipolar affective disorder associated with dangerous episodes of self-injurious and aggressive behaviors placing his caregivers and himself at significant safety risk. Extensive behavioral and medication interventions in both inpatient and outpatient settings had been ineffective, and the boy was at risk for acute physical injury and restrictive out-of-home placement. An acute course of eight bilateral electroconvulsive therapies resulted in significant mood stabilization and significant improvement of self-injury and aggression. Maintenance electroconvulsive therapy and psychotropic interventions were then pursued. No ECT-related complications have been reported in any of the case series in which ECT was utilized to treat SIB and aggressive behavior to date.

4.4.3.9   Water Mist Spray

The use of water mist spray is considered to be a type of aversive conditioning and/or punishment. Typically the stimulus involves spraying water directly into the face of the individual, which is often perceived as an aversive event. The first use of this procedure was reported by Peterson (1968) who evaluated its effectiveness as a treatment for SIB in a severely retarded boy. The technique of water mist spray was discovered somewhat serendipitously as this boy's mother reported that she had reduced his tantrums by pouring water on him. Subsequently, Peterson and Peterson (1977) evaluated the effects of response-contingent water as a punisher and demonstrated some reduction of SIB in a developmentally disabled boy. However, complete suppression of SIB was not achieved.

Merwin and Kornegay (1977) used water mist spray in the treatment of a variety of SIB's in a profoundly retarded girl. Each occurrence of SIB was followed by a verbal reprimand and water, in the form of a fine mist, was sprayed into the patient's face. Their results demonstrated a rapid decrease in SIB and the patient was subsequently able to receive positive reinforcement for engaging in appropriate behavior. Murphy et al (1979) reduced self-choking with response-contingent water and reinforcement for alternative behaviors in a profoundly developmentally disabled boy. Dorsey et al (1980) evaluated the effects of water mist spray on SIB in seven profoundly developmentally disabled persons

with hand-biting, skin tearing and head-banging. Similar to previous studies, there was substantial reduction but not complete elimination of SIB.

Singh et al (1986) compared the effect of water mist spray with either facial screening or contingent exercise. Water mist spray was as effective as facial screening in suppressing face-slapping; however, it was not as effective as facial screening for finger-licking or forced arm exercise for excessive ear-rubbing. These results suggest that while water mist spray is effective, it may be less so than alternative procedures.

Overall, the use of water mist spray may be an effective technique for reducing SIB; however, various parameters for the most effective use of this technique (e.g., frequency of sprays, water temperature, distance to face, etc.) have yet to be investigated.

4.4.3.10 Bitter Substances

Similar to physical restraint and water mist spraying, bitter substances have been used as aversive stimuli in the treatment of maladaptive behavior in young children. Mayhew & Harris (1979) demonstrated the effectiveness of lemon juice in treating face-punching and head-banging in a profoundly developmentally disabled boy. A small amount of lemon juice was squirted into the patient's mouth each time he engaged in a self-injurious act. However, the total amount of lemon juice per day was restricted to a relatively small amount to avoid potential medical complications of excessive citric acid ingestion. There have been virtually no studies reporting the use of bitter substances to treat SIB and aggressive behavior since the late 1970's.

4.4.3.11 Facial Screening

Facial screening is considered to be a mildly aversive stimulus that has been used as a "punisher" to modify a variety of maladaptive behaviors in children, including SIB and aggressive behavior. There are several variations of facial screening. The most common include covering the patient's face with some type of covering, usually a terrycloth bib, for a few seconds following a self-injurious or aggressive behavior (Singh, 1981). Lutzker (1978) reported the effects of facial screening on head- and face-slapping in a 20 year developmentally disabled male. Following each occurrence of the SIB, the therapist verbally reprimanded the patient for engaging in the SIB and then quickly put the bib over his face and head and held it loosely until the SIB stopped. This technique proved effective in reducing but not eliminating SIB. Zegiob et al (1978) treated multiple SIB's in a profoundly developmentally disabled boy who also had brain damage. They found that the suppressive effects of facial screening generalized to both SIB and aggressive acts.   Of interest, after repeated administrations of the facial screening technique, the authors found that simply presenting the bib without actually covering the patient's face was not effective in reducing SIB and aggressive behavior.

Watson and colleagues (1986) examined the effects of following the self-injurious finger-sucking of two profoundly mentally retarded persons by 5 seconds of either visual or facial screening were compared using an alternating treatments design. The two screening procedures reduced the self-injury more than did a no-treatment control condition. Visual screening was more effective than facial screening with one of the subjects. Subsequently, when the only treatment was visual screening, the contrast in the effect on self-injury between visual screening and no-treatment was further increased.

4.4.4 Summary of Benefits and Risks of Treatments for SIB and Aggressive Behavior

Treatment of SIB and aggressive behavior essentially falls into two broad categories, pharmacological and behavior. Currently, there are no published consensus guidelines or practice parameters for the treatment of SIB and aggressive behavior for individuals with limited intellectual ability or development disabilities. Review of the published literature suggests that behavioral treatments should be the first line treatment, notably when environmental factors contributing to occurrence of SIB and aggressive behavior can be identified. However, there does not appear to be any consensus in the literature regarding the type of behavioral intervention that should be employed first. Pharmacological interventions are typically used in conjunction with a behavioral treatment program or when patients do not respond to a behavioral therapy.

With the exception of the studies which investigated opioid agonists and clomipramine, the majority of the pharmacological and behavioral treatment studies are largely confined to small sample sizes or single case reports. Few studies are controlled studies or comparative investigations. Despite the numerous methodological limitations of these studies, overall both pharmacological and behavioral interventions appear to be relatively successful in reducing but not completely eliminating SIB and aggressive behavior in persons with intellectual and developmental limitations. This may largely be attributable to the fact that the majority of these studies are limited to either a single case report or a small case series in which a beneficial effect of the treatment was found. Reporting of adverse events, with the exception of pharmacological studies, is sparse, and few behavioral studies report adverse events. The only exception is for the use of extinction in which there is the potential risk of so-called extinction bursts which is an upsurge, particularly in the early stages of the intervention, of the actual undesired or unwanted behavior. If this upsurge in behavior poses a danger to the individual and/or others, then an extinction paradigm is not a feasible option (Lerman et al, 1999).

Recently, Matson and colleagues (2011) suggested guidelines for the treatment of SIB and aggressive behavior in individuals with autism spectrum disorders. However, these guidelines are not "evidence-based" and represent the authors

assessment of the effectiveness of the available published literature. The suggested guidelines include,

- A functional assessment should be employed to determine whether clear environmental causes are evident. Research shows that environmental variables may account for up to 80% of challenging behaviors in adults with intellectual disabilities (Matson et al, 1999).

- Where environmental factors are not evident, medication should be considered. However, broad-based and comprehensive side-effect evaluations need to be completed periodically during drug administration, and even more frequently during drug titrations and increases in dosage. Medication should be a temporary solution. As behavioral treatments may take some time to lead to behavioral change, medication may be needed in the short term, but then may be able to be faded out with the continued use of behavioral strategies.

- Treatment of SIB and aggressive behavior in persons with intellectual or developmental limitations should be multidisciplinary.

- Individuals with intellectual impairment and developmental disabilities have varying levels of cognitive ability which must be considered in determining possible treatment interventions. For example, persons with severe to profound mental retardation lack the cognitive capacity to understand the relationship between their behaviors and the reinforcement contingency be it positive or negative that is applied. For some individuals, principles of classical conditioning in which a conditioned response is learned (i.e., not to engage in SIB and aggressive behavior) may need to be applied. For these cases, aversive techniques such as restraint, ammonia, facial screening, etc. may be more effective than traditional reinforcement schedules used in cognitively intact persons.

5   Benefits and Risks of ESDs for Aversive Conditioning

This section examines specific information regarding benefits and risks based on adverse event/complaint reports to public agencies, prior reports, reviews and public proceedings that have been provided to FDA or discovered by the FDA. The statute and regulations require FDA to consider "all available data and information" in making a banning determination.[20] Data and information were considered from various sources. Two systematic literature reviews were performed by the FDA to identify the benefits and risks associated with the use of ESDs for aversive conditioning that fall within the scope of the proposed ban. The review of benefits focused on self-injurious behavior (SIB) and aggressive behavior. FDA believes the adverse events reported for ESDs for Aversive Conditioning may be generalizable across indications, and therefore information regarding AEs from other indications is presented for panel consideration.

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[20]   21 U.S.C. § 360f(a); 21 CFR § 895.21(a)(3)

Most of the literature identified pertained to SIB for developmental disabilities; other medical indications for use of ESD's for Aversive Conditioning as reported in the literature include the following:

- Alcohol and other substance abuse/dependence
- Assaultive/destructive behavior associated with psychiatric disorders/developmental disabilities
- Cerebral Palsy
- Smoking cessation
- Schizophrenia
- Severe Obsessive-Compulsive Disorder
- Trichotillomania
- Weight Loss

5.1 FDA Systematic Literature Review

FDA conducted a systematic literature review to assess the benefits and risks of ESDs for aversive conditioning.

5.1.1 Methods

Separate searches were conducted to examine the published literature for the treatment effect and the adverse events associated with ESDs for Aversive Conditioning. Electronic searches were undertaken of EMBASE (1980-present), MEDLINE (1966-present), and PsycINFO.   Search results were limited to "English" and "human".

For treatment effect, we searched the databases using the Medical Subject Headings (MeSH) term "treatment outcome" AND the following device identifiers: "graduated electronic decelerator" OR GED OR "self injurious behavior inhibiting system" OR SIBIS OR "stimulatory sonic control" OR "whistle stop" OR "electrical stimulation" OR " electrical skin shock" OR "electric shock" OR "electric skin shock" OR "aversive conditioning" OR " aversive shock" OR "aversive stimulus" OR "aversive stimuli" OR "aversive treatment" OR "aversive control" OR "aversive conditioning treatment" OR "aversive electrical treatment" OR "electrical aversive treatment" OR "electrical aversive conditioning" OR "aversion therapy" OR "electrostatic shock" OR "contingent shock" OR "response contingent shock" OR " contingent electric stimulation" OR "contingent electric stimulus" OR "contingent electric stimuli" OR "therapeutic shock device" OR "behavioral decelerator" OR " punishment" OR "operant conditioning" OR "noxious stimulation" OR "noxious stimulus" OR "noxious stimuli" OR "noxious conditioning" OR "behavioral reduction".

A similar search strategy was employed for adverse events but because of the large number of returned results, the strategy was modified. We searched the databases using the MeSH terms, "adverse effects" OR "side effects" OR "undesirable effects" OR "injurious effects" AND the following device identifiers, "graduated electronic decelerator" OR GED OR "self injurious behavior inhibiting system" OR "SIBIS" OR "stimulatory sonic control" OR "whistle stop" OR "electroshock" OR "contingent

shock" OR "punishment" OR "operant conditioning" OR "electrical skin shock" OR "electric shock" OR "electric skin shock" or "aversive conditioning" OR "aversive shock" OR "faradic" OR "electrodermal" OR "therapeutic shock device". We excluded articles that contained the following terms: "ECT" OR "electroconvulsive therapy" OR "eating disorder" OR "anorexia" OR "incontinence" OR "FES" OR "functional electrical stimulation" OR "acupuncture" OR "defibrillator" OR "cochlear" OR "nerve stimulator" OR GES OR "gastric electrical stimulation" OR VNS OR "vagus nerve stimulation" OR biofeedback OR "brain stimulation" OR "audiometry" OR "analgesia" OR "anesthesia".

The articles were reviewed for relevance to the review. Title and abstract review was independently conducted for each search by two review team members and potentially relevant articles were obtained. Any disagreements between the two primary reviewers were adjudicated by the entire review team. In addition to the systematic searches of the three databases (including review of the two search results for both benefits and risks) , other potentially relevant articles were identified from other sources, including information submitted to FDA, prior public proceedings on the subject and bibliographies of articles identified in the original search strategy.

Overall, the search yielded 57 articles (12 reviews, 45 clinical reports) regarding treatment outcome and 39 articles (12 reviews, 27 clinical reports) regarding adverse events. These articles were reviewed in full for information on the benefits and risks (respectively) of ESD for aversive conditioning for SIB and aggressive behavior.

5.1.2   Benefits Identified through FDA Literature Search

Articles were reviewed for clinical information regarding the use of ESD's for aversive conditioning to treat SIB or aggressive/destructive behavior. No randomized controlled trials were identified. A total of 45 studies were identified, and include the following:

- Forty-one case reports/case series;
- One case-control study conducted outside the U.S.;
- One within subjects comparison trial conducted outside the U.S.;
- One retrospective review of 60 patient charts conducted in the U.S.; and
- One questionnaire follow-up study of 22 subjects (11 responded) who had received ESD for aversive conditioning conducted in the U.S.

There were twenty-six articles published before 1980, twelve articles published from 1980-2000, and seven articles published since 2000. Only three groups of U.S. researchers have published in this area since 2000.

The highest quality publication was a case control study by Duker and Seys (2000). They conducted a prospective case control study of 8 subjects with SIB compared with 8 matched controls. The primary outcome measure was amount of mechanical restraint required for each subject. Though no statistical analysis was conducted, the author reported an 82% decrease in mechanical restraint (over an 8 year period) for subjects receiving ESD. Limitations of the study are that the primary outcome measure did not

directly examine SIB and no statistical analysis was conducted.

The other comparative report was of a within subjects investigation at baseline and with the ESD applied. Duker and Van der Munckhof (2007) examined the heart rate of 5 individuals being treated for severe SIB with ESDs. They noted that when individuals were wearing an active ESD their heart rate was significantly lower than when they were not. They concluded that individuals were less anxious when an active device was applied. Limitations of this study are that heart rate has not been demonstrated to be a valid marker of anxiety. Moreover, the association of heart rate or anxiety with SIB has not been established.

Israel et al. (2008) conducted a retrospective chart review of 60 patient charts at a special needs education facility who had received ESD for aversive conditioning as part of their treatment program. They reported use of two different devices, the GED-1 and GED-4.[21] They concluded that ESD use as a supplement to positive programming was effective (defined as a 90% or greater reduction from baseline) in 100% of patients.

Murphy and Wilson (1980) conducted a follow-up study of subjects who had received ESD for aversive conditioning. They sent questionnaires to 22 identified subjects and received 11 responses. Reviewing the responses, they found that relapse, defined as a "marked increase in self-injurious behavioral after treatment ended" occurred in seven of eleven successfully treated patients within two years after treatment ended. Two subjects showed continued suppression of SIB symptoms.

Forty-one case reports/case series (n= 105 subjects) containing specific clinical report information were identified (See Table 3 below).

The case reports/case series are generally supportive of the effectiveness of ESDs for SIB and aggressive/destructive behavior. However, in many cases, use of ESDs for aversive conditioning occurs in conjunction with other treatments (e.g., positive treatment programs, behavioral and functional treatment programs, medications); therefore it is not possible to assess the treatment effect due to the ESD alone.

Additionally, many reports only assess short-term effects or do not specify the length of follow-up assessment. Fourteen studies (n=29) report assessment of six months or less while eight studies (n=25) do not specify length of follow-up assessment. Eighteen studies (n=51) do report results past six months with one case report showing benefit out to five years. Of those, twelve reported long-term benefits (past six months), though some reported maintenance use (continued periodic application of ESD) or the use of other treatments during the assessment period. One article (Bruhl, et al, 1982) noted mixed results; of seven subjects, four had near complete suppression of SIB with in the

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[21] GED 1, average current 15 mA RMS, 60 V RMS when applied to a resistor of 4kOhm, 2 sec train of direct current square waves with duty cycle of 25% and pulse repetition frequency of 80 pulses per second. GED-4, average current of 41 mA RMS 66 V RMS when applied to a resistor of 1.6kOhm, 2 sec train of direct current square waves with duty cycle of 25% and pulse repetition frequency of 80 pulses per second.

first 2 weeks and the effect was sustained by occasional "booster" shocks for 1-2 year follow-up periods. Three showed "partial or transitory" results; for two of those, reinstitution of contingent shock treatment was not successful. In another article examining inpatient use of ESD in conjunction with a variety of behavioral and functional treatments over three years (Browning, 1971), for SIB, there was complete response in one and partial response in one subject. For aggressive behavior, there was complete response in two subjects and partial response in three subjects. Even after 35 months in the intense behavior modification program, response approximations of previously extinguished behavior were still elicited. The authors concluded that, "…to maintain a child's behavior at the level occurring at date of discharge would require very close to a one-to-one supervision in structured activities, in order to retain the child's attention, newly acquired behaviors and to prevent the retrieval of those habits which had been extinguished."

One study noted that initial effectiveness and overall duration of effect may be related to stimulus intensity (Williams, Kirkpatrick-Sanchez, and Iwata, 1993), while another article that demonstrated effects up to 8 years (Duker and Seys, 2000) concluded loss of effect of previous reports was due to the use of lower level stimulation. These findings suggest that effectiveness and duration of effect may be dose-dependent (i.e., higher intensity stimulation is associated with greater effectiveness and longer duration of effect).

Table 3: Summary of Articles Reviewed for Benefits Associated with ESDs for Aversive Conditioning

(Note, **bolded** devices are FDA cleared (see Table 1))

Reference	Study Type[1]	Number of Subjects	Age[2] (years)	Diagnoses[3]	Device[4]	Effectiveness
Bail, Sibbach, Jones, Steele and Frazier 1975	CS	5	7, 11, 13, 30, 35	MR, Down Syndrome, SIB, Aggression	"accelerometer activated electronic pulse generator"	Subject 1 had decrease in SIB over 2 years, required occasional use (-7 times over 2.5 months) or daytime use to maintain decrease in SIB. Subject 2 had good initial response, then after 4 months, increase in SIB requiring mechanical restraint, adapted to shock. Subject 3 had significant decrease in SIB, with one episode of brief regression, over 1 year. Subject 4 had significant initial decrease in assaultive behavior, with 3-4 recurrences over 3 years. Subject 5 had initial significant decrease in assaultive behavior which then began to increase again after 2 years. Concurrent use of positive behavior modification programs.
Baroff and Tate, 1968	CR	1	9	Blind, Autism, SIB	NS	Each SIB was followed by a 130-v. electric shock delivered to S's thigh by a cattle prod. During a 24-min. observation period prior to the introduction of the punishment, 5 emitted self-injurious responses at the rate of 2.0/min. During the next 90 min. of contingent punishment, only five self-injurious responses occurred at a rate of 0.6/min. Short-term report only.
Birnbrauer, 1968	CR	1	14	Autism, MR, Aggression	Sears stock prod 150-300 mA (peak) 500 V @ 500 Kohm	ESD results in rapid and powerful suppression. No generalization to conditioned verbal warning (verbal warning alone not effective). Unclear duration.
Brandsma and Stein, 1973	CR	1	24	MR Assaultiveness	Hot Shot Sabre Six[5] 1400 V peak 0.5 mA,	Reported effective with twice daily 30 min sessions over 5 days.

Reference	Study Type[1]	Number of Subjects	Age[2] (years)	Diagnoses[3]	Device[4]	Effectiveness
Browning, 1971	CS	5	3-11	Autism, SIB	"high voltage, low amperage"	Complete response of SIB in 1 subject, partial response in 1 subject. Complete response of aggressive behavior in 2 subjects and partial in 3 subjects. Even after 35 months in the intense behavior modification program encompassing the entire day of the child, response approximations of previously extinguished behavior were still elicited. Shock used in conjunction with a variety of behavioral and functional treatments
Bruhl et al., 1982	CR	7	NR	SIB	NR	4 subjects had near complete suppression of SIB with in the first 2 weeks and effect sustained by occasional "booster" shocks for 1-2 year follow-up periods. 3 subjects showed "partial or transitory" results. For 2 of 3 with partial or transitory response, reinstitution of contingent shock treatment program was not successful.
Bucher and King, 1971	CR	1	11	Schizophrenia	Hot Shot stock prod 150-300 mA (peak) 200-500 V	Suppression of target behaviors. Able to discriminate which target behaviors would be punished. Generalization to other behaviors and conditions. Data do not indicate long-lasting suppression.
Bucher and Lovaas 1968	CS	2	7, 7.5	MR, SIB	NS	Brought rate of SIB to zero, stopped avoiding adults, cried less, less restraint, unclear duration, initially did not generalize to other treaters.
Callias, 1974	CR	1	4	MR, SIB	NS	Rapid decline of SIB to zero. Fading after SIB completely eliminated, remains without SIB. Concurrent treatment with positive reinforcement.
Corte et al., 1971	CS	4	17-20	MR, SIB	Hot Shot	Electric shock punishment eliminated SIB in all 4 subjects for up to 3 months. However, the effects of the punishment were usually specific to the setting in which it was administered.

Reference	Study Type[1]	Number of Subjects	Age[2] (years)	Diagnoses[3]	Device[4]	Effectiveness
Duker and Seys, 1996	CS	12	NS	MR, SIB	HSP 3012 40 mA 30 Hz impedance range, 1-7 kΩ	7 patients had nearly complete suppression of SIB, physical restraints no longer necessary; 3 patients had moderate effects and substantial decrease of imposed physical restraint, required daily administrations of electrical aversive stimuli; 2 patients SIB not suppressed. Duration 2-47 months
Duker and Seys, 2000	CC	8 (with matched controls)	NS	SIB	HSP3012	Mechanical restraint decreased in the electrical aversion treatment group over approximately 8 years (with and without maintenance treatment). Estimate of 82% effectiveness, no statistical analysis.
Duker and Van der Munckhof, 2007	Obs	5	NS	SIB	42 mA 30 or 60 Hz	Active treatment yielded statistically lower mean heart rate (HR) than not wearing it. HR presented as a marker for stress/anxiety, only acute effects observed.
Foxx et al., 2003	CS	4	NS	Aggression	NS	Effectiveness reported from comprehensive behavioral programs including ESD. Effectiveness not defined. Duration 1 to 15 months.
Foxx, Bittle, and Faw, 1989	CR	1	20	Aggression	NS	All forms of aggression were nearly eliminated within 1 month, and these effects were maintained for 14 additional months. Shock eventually replaced with other treatments.
Griffin, Locke, and Landers, 1975	CR	1	NS	SIB	NS	Total suppression of SIB across all settings over 34 months. Hair tug first resulted in partial suppression, then ESD suppressed even more.
Hall et al., 1973	CR	1	11	MR, SIB	Shock stick	By day 5, SIB reduced to 0 and emotionality had returned to pre-treatment levels, but SIB returned when shock-stick not present. Duration 38 days.

Reference	Study Type[1]	Number of Subjects	Age[2] (years)	Diagnoses[3]	Device[4]	Effectiveness
Israel et al., 2008	RA	60	NS	Aggression	**GED-1,** 15 mA rms 60 V rms @ 4 kΩ 80 pps 2s GED-4, 41 mA rms 66 V rms @ 1.6 kΩ 80 pps 2s	ESD as a supplement to positive programming, Reported effective (defined as a 90% or greater reduction from baseline) with 100% of the participants, when ESD is used as a supplement to positive programming. Duration up to 3 years.
Israel et al., 2010	CS	7	NS	Severe Treatment Resistant Behavior Problems	**GED-1** GED-3A GED-4	All subjects had improvement with GED up to 21 months.
Linscheid, Haertel, Cooley 1993	CS	3	11-16	MR, autism, SIB	**SIBIS** 85 V 3.5 mA avg 0.2 s	At 5 years, one subject continues to have SIB at problematic rates, one has a zero rate after 2 years with constant wearing of device (and device was being faded), one subject initially had a 90 % suppression rate, when then increased again with inconsistent application, and then decreased again with consistent application (continuous wearing of device over 5 years).
Linscheid and Reichersbach, 2002	CR	1	15	SIB	**SIBIS**	Dramatic response of SIB with functional analysis to contingent electric shock up to 5 years.

Reference	Study Type[1]	Number of Subjects	Age[2] (years)	Diagnoses[3]	Device[4]	Effectiveness
Linscheid et al., 1990	CR	5	NS	SIB	**SIBIS**	Subject 1, bites, hair pulls and hits to chair reduced whereas pinches increased. Subject 2, Large, immediate, and sustained decreases in head hitting were observed upon introduction of SIBIS. SIB returned to baseline when SIBIS inactive. Subject 3, baseline 100% head hitting (at least once per second), SIBIS device resulted in 0% head-banging, SIBIS inactive device resulted 64%. Subject 4, significant decrease in head hitting with SIBIS active, continued head hitting SIBIS inactive. Subject 5, near elimination of head banging with active, significant reduction with SIBIS inactive.
Linscheid et al., 1994	CR	1	8	MR, CP. microcephaly	**SIBIS**	Large decrease in SIB, increase in positive behaviors, possible increase in crying with SIBIS, over unclear period of time.
Lovaas, Schaeffer and Simmons, 1965	CS	2	5	Schizophrenia, self-stimulation, tantrums	Harvard Inductorium	Immediate decrease in self-stimulation and aggression and replacement with social behaviors. Duration 1 month.
Lovaas and Simmons, 1969	CS	3	8, 8, 11	MR, psychosis, SIB	Hot Shot 1400 V peak @ 50,000 Ω 1 s	SIB immediately suppressed, recurred when shock was removed. Suppression was selective, both across physical locales and interpersonal situations, as a function of the presence of shock. Generalized effects on other non-shock behaviors, appeared in clinically desirable direction. Duration up to 1 year.
Ludwig, Marx, Hill and Browning, 1969	CS	1	31	Schizophrenia, assaultive	Hot Shot Sabre Six 1400 V 0.5 mA	Sharp reduction in assaultive behavior. Unclear duration.
McFarlain, Andy, Scott and Wheatley, 1975	CR	1	25	MR, SIB	Hot Shot stock prod, model DB	Shock and paired "no" effective to decrease head banging, "No" effective with occasional paring with electric shock. Only short –term reported.

Reference	Study Type[1]	Number of Subjects	Age[2] (years)	Diagnoses[3]	Device[4]	Effectiveness
Merbaum, 1973	CR	1	12	Autism, SIB	Hot Shot stock prod 150-300 mA (peak) 200-500 V	Administration by mother, therapist. Near complete reduction of SIB to 1 year.
Miron, 1971	CS	11	NS	NS	NS	Shock significantly decreased SIB, but did not eliminate it completed (with shock alone). The most crucial aspect of this program is not the shock punisher, rather the reinforcement of behaviors incompatible with SIB. Suppressive effects of aversive shock tend to be temporary, and SIB reduced solely through aversive stimuli can be expected to return when the aversive circumstances are removed, unless precautions are taken to reinforce other responses incompatible with SIB.
Mudford, Boundy and Murray, 1996	CR	1	36	MR, SIB	TSD, Hot Shot Sabre Six	TSD (therapeutic shock device 0.8 mA, 2 A peak, 640 V peak, 5.5 µs duration, 61 mJ)-reduction of 10 events/min to 0.02 events/min, as effective as the higher output HSSS. Duration short-term only.
Murphy and Wilson, 1980	Questionnaire follow-up	22	NS	NS	NS	Questionnaire study of individuals reported in case studies. 22 subjects, 11 responders. Relapse, defined as a "marked increase in self-injurious behavior after treatment ended" occurred in 7 of 11 successfully treated patients within 2 years after treatment ended. 2 subjects showed continued suppression.
Muttar, 1975	CR	1	10	Dev. Delay, SIB	300 V, 2 mA, 0.5 sec	Elimination of SIB was virtually complete at 3 months, no SIB for 20 months. With other staff, however, aggressive nipping and biting remained frequent (no generalization to other staff).
Prochaska et al., 1974	CR	1	9	MR, seizures	A Farrall A-V-2 shocker 2 mA pulsating 0.5 s	After approximately 3 months, head banging reduced to zero, but then increase in head-snapping (symptoms substitution), which was then reduced to zero after 2.5 months, and has been eliminated for 7 months. Concurrent reinforcement of incompatible behavior.

Reference	Study Type[1]	Number of Subjects	Age[2] (years)	Diagnoses[3]	Device[4]	Effectiveness
Ricketts and Goza, 1993	CR	1	28	MR, SIB, epilepsy	**SIBIS**	Initial effectiveness from 2600 responses/hr to 1 response/hr, but then loss of effectiveness after 31 months, self-injury was increasingly characterized by episodic "bursts", eventually reaching the point that it became impossible to maintain him in SIBIS for any extended period of time.
Risley, 1968	CR	1	6	Diffuse brain damage, SIB, aggressive behavior	NS	Initial decrease in SIB accompanied with increase eye contact, then substituted with chair climbing, which was then also successfully treated with ESD. Concurrent use of behavioral/functional treatments. Duration 51 days.
Romanczyk and Goren, 1975	CR	1	6.5	Autism, SIB	NS	Shock only 6 sessions rate of SIB decreased from 4500/hr to 300/hr. Shock, response prevention and differential reinforcement of behavior for 12 sessions led to dramatic reduction in rate and severity of SIB. Near complete reduction of SIB over 40 days. SIB returned as soon as device removed. Effectiveness was lost after 2 months.
Salvy et al., 2004	CR	1	3	Partial trisomy, DD, SIB	**SIBIS**	Effective in suppressing head banging to 7 months
Simmons and Reed, 1969	CR	1	5	MR, SIB	NS	Self-hitting decreased to 0, effective seen over 8 months with admonishing words and periodic shocks.
Tate and Baroff, 1966	CR	1	9	SIB	Stock prod (Sears & Roebuck #325971) 130 V	Immediate reduction of SIB, and continued effectiveness with ESD administration over 167 days. Other punishments (i.e., withdrawal of physical contact) also appeared effective. Appears to be same case report as Baroff and Tate, 1968.
Van Oorsouw et al., 2008	CS	9	8-30	SIB, aggressive behavior	**GED-1**	Short term effectiveness pre- post-treatment was demonstrated; no statistical analysis. "Positive side effects are probably more common than negative side effects."
Whaley and Tough, 1968	CR	1	6	MR, "mongoloid", SIB	65 V, 1 mA pulsating DC current	Positive reinforcement strategy, shock removed when target behavior (touching toys; incompatible with SIB) was performed. Immediate reduction in SIB, generalized to other toys.

Reference	Study Type[1]	Number of Subjects	Age[2] (years)	Diagnoses[3]	Device[4]	Effectiveness
Williams, Kirkpatrick-Sanchez, and Crocker, 1994	CR	1	22	MR, autism, SIB	**SIBIS**	SIBIS attained significant reductions, 99.5% reduction from baseline (16.6 responses per minute), but rates began to climb again to a lower rate than baseline (after cessation of shock) until a SIBIS pairing procedure could be applied more consistently (with self-injury). This approach presented an estimated 1650 applications of mechanical restraint, and reduced dose of Loxitane. 6 months of daily treatment (4 times x 10 minutes) paired with other treatments, no shock for 5 months and then maintenance treatment over 7 years (total).
Williams, Kirkpatrick-Sanchez, and Iwata, 1993	CR	1	NS	MR, SIB	**SIBIS** Hot Shot Power Mite	SIBIS minimal reductions in SIB (reduction of 28% biting, 48% other), Hot Shot immediate and large reductions in SIB (99% reduction). Relapse after 6 months.
Yeakel et al., 1970	CR	1	14	Autism, SIB	bonnet→arm shock	Wearing device bonnet stopped head banging, but when removed, SIB returned
Young and Wincze, 1974	CR	1	21	MR, SIB	Lehigh Valley Electronics (551-13) 15-20 Hz 0.5 s 700 V	Head-banging punished, not head hitting, head-banging reduced to near zero, head hitting continued.

[1] CR, case report; CS, case series, RA, retrospective analysis; CC=Case control.

[2] NS, not specified.

[3] MR, mentally retarded; SIB, serious injurious behavior; SRBP, serve resistant behavior problems; CP, cerebral palsy; DD, developmentally disabled.

[4] NS, not specified; TSD, therapeutic shock device. Note that only the devices, as specified in Section 3.2, have been cleared by the FDA (e.g., SIBIS and GED-1 (same as GED)).

[5] Twice daily 30 minute sessions for 5 days.

In addition to the publications in Table 3 that included specific clinical information on individual subjects, the following twelve review articles (without new clinical information) examining effectiveness of ESDs for Aversive Conditioning for various etiologies were evaluated:

- Azrin and Holz, 1966 (Problematic Behaviors)
- Bachman, 1972 (SIB)
- Corbett, 1975 (SIB)
- Logan and Turnage, 1975 (Behavior Problems - General)
- Lichstein and Schreibman, 1976 (Autism)
- Franke and Simmons, 1976 (Schizophrenia and Mental Retardation)
- Carr and Lovaas, 1981 (Severe Behavioral Problems)
- Singh, 1981 (SIB)
- Foxx, Plaska and Bittle, 1986 (Aberrant Behaviors including SIB)
- Lernan and Vorndran, 2002
- Meyers and Evans, 1989 (Behavior Problems - General)
- Eikeseth, Lovaas and Holden, 2006 (Aberrant Behaviors)

These reviews generally supported the conclusion that ESDs for aversive conditioning for SIB and aggressive/destructive behavior demonstrate short-term effectiveness. Lichstein and Schreibman (1976) conducted a literature review specifically examining reports of using ESDs in autistic children. They noted that "…in all of these studies, electric shock proved to be a highly effective therapeutic agent with autistic children" and estimate that positive effects compared to negative effects occurred at a ratio of 5, 1. They also reported that the lack of long-term durability as well as setting specificity of results may be an obstacle to overall satisfactory effect. In terms of positive side effects, they included "Response Generalization", an increase in "Social Behavior", and "Positive Emotional Behavior". Negative side effects are discussed in Section 5.1.3, below.

A number of reviews specifically examined long-term effectiveness (Logan and Turnage, 1975; Lichstein and Schreibman, 1976; Franke and Simmons, 1976). One review (Lernan and Vorndran, 2002) concluded that ESD may have long-term effectiveness while Logan and Turnage (1975) noted that the effect appeared to be short-term only (i.e., symptoms are only "momentarily suppressed"). Franke and Simmons (1976) in a comparison of different treatments for controlling behavior in individuals with mental retardation or schizophrenia noted that in terms of immediate effects, "punishment was the quickest means of suppressing behavior." (page 517) For longer-term effects, time-out programs fared the best, followed by differential reinforcement techniques. "In marked contrast to [short-term effects], punishment and extinction programs seemed to have the least durable success." (pages 517-518).

In summary, the literature review generally supports short-term benefit of ESD for aversive conditioning for SIB and/or aggressive behavior. The long-term benefits are less well established. The role of stimulus intensity and the use of other concurrent treatments are not well understood, but may significantly impact study results.

Limitations of this review include the fact that the majority of articles were case reports/series, published in the 1960s and 1970's (prior to modern publication standards), and consequently do not adhere to established study conduct and reporting standards. No comparison trials directly examining ESDs for SIB and/or aggressive behavior were identified and the one prospective case control study examining ESD for SIB did not use a direct measure of SIB as the primary outcome (i.e., primary outcome was a decrease in mechanical restraint) and did not conduct a statistical analysis.

5.1.3 Risks Identified through FDA Literature Search

Articles were reviewed for reports and/or assessment of risk (See Table 4). Twenty-eight studies were identified. Adverse events were reported in one prospective case-control trial and one retrospective chart review of 60 patients. Twenty-six case reports/series (encompassing 66 subjects) also provided an assessment of AEs, while 16 other case report/series did not mention assessing AEs or the occurrence of AEs. One within subjects' comparison (baseline vs. treatment) of heart rate also made no mention of AEs or of systematic assessment of AEs (Duker and Van der Munckhof, 2007).

As with the effectiveness review, the highest quality publication was a case control study. Duker and Seys (2000) conducted a prospective case control study of 8 subjects receiving ESD for SIB compared with 8 matched controls (not receiving ESD). While there was no systematic report of AEs by subject, the authors mentioned that a "few problems that may be encountered during the often extended course of treatment are that individuals may adapt to the intensity of the electrical stimulus, that self-restraint may emerge or may intensify, that individuals may show SIB at very low intensities that eventually results in tissue damage, etc." (page 241).

One retrospective review of 60 subjects noted only one negative side effect "temporary discoloration of the skin that cleared up in a few minutes or days." (Israel et al., 2008) However the authors also went on to clarify, "temporary emotional behaviors, a temporary tensing of the body, or attempts to remove the device or grab the transmitter noted during treatment were classified as 'immediate collateral behavior' and were not considered adverse events." (Israel et al., 2008)

Review of the case studies/series found that twenty-six articles (n=66 subjects) reported the assessment for the occurrence of an AE. Six articles (n=11) noted that AEs were not observed in their subject population.

Table 4: Articles Reviewed for Adverse Events Associated with ESDs for Aversive Conditioning for Patients with SIB and Assaultive/Destructive Behavior associated with Developmental Disabilities
(Note, **bolded** devices are FDA cleared (see Table 1))

Reference	Study Type[1]	Number of Subjects	Age[2] (years)	Diagnoses[3]	Device[4]	Reported Adverse Events
Bail, Sibbach, Jones, Steele and Frazier 1975	CS	5	7,11,13, 30,35	MR, Down Syndrome, SIB, aggressive	NS	Overall there was little to suggest the development of adverse side-effects.
Birnbrauer, 1968	CR	1	14	Autism, MR, Aggressive behavior	Sears stock prod (32 AF 5971) 150-300 mA (peak) 500 V @ 500 KΩ	Symptom substitution (e.g., incontinence, napkin tearing), escape behavior.
Brandsma and Stein, 1973	CR	1	24	MR Assaultive	Hot Shot Sabre Six	No tissue damage or other physical problems, but possible hostility and retaliation
Bucher and King, 1971	CR	1	11	Schizophrenia	Hot Shot stock prod 150-300 mA peak 200-500 V	Anticipatory fear and avoidance (of experimenter's initial movements to shock)
Bucher and Lovaas 1968	CR	2	7, 7.5	MR, SIB	"1 sec shocks"	• "painful but physically harmless" • Aggression, crying and shivering.
Duker and Seys, 1996	CS	12	NS	MR, SIB	HSP 3012	Panic, extreme anxiety (i.e., screaming, crying, attack, escape); 1 subject "froze by refraining from showing any sort of behavior"
Duker and Seys, 2000	CC	8 (with matched controls)	NS	SIB	HSP 3012	No systematic report. Problems noted, • adaptation to stimulus • self-restraint may emerge or may intensify • individuals may show SIB at very low intensities that eventually results in tissue damage
Hall et al., 1973	CR	1	11	MR, SIB	Shock stick	• Initial reaction was an increase in emotionality and frequency of self-mutilative behaviors. • Increased incontinence (possible symptom substitution)

Reference	Study Type[1]	Number of Subjects	Age[2] (years)	Diagnoses[3]	Device[4]	Reported Adverse Events
Israel et al., 2008	RA	60	NS	Aggressive behavior	**GED-1** GED-4	• Temporary discoloration of the skin that cleared up in a few minutes or days. • Temporary emotional behaviors, a temporary tensing of the body, or attempted to remove the device or grab the transmitter noted during treatment were classified as "immediate collateral behavior" and were not considered AEs.
Linscheid and Reichersbach, 2002	CR	1	15	SIB	**SIBIS**	No short- or long- term negative side effects
Linscheid et al., 1990	CR	5	NS	SIB	**SIBIS**	No AEs (2 subjects) No systematic report (3 subjects)
Linscheid et al., 1994	CR	1	8	MR, CP. microcephaly	**SIBIS**	Possible increase in crying
Lovaas, Schaeffer and Simmons, 1965	CS	2	5	Schizophrenia, self-stim, tantrums	Harvard inductorium	Fear of device. Decrease in happiness and contentment, increased dependency.
Lovaas and Simmons, 1969	CS	3	8,8,11	MR psychosis	Hot Shot	Temporary aversion to experimenter, aversion to device
Ludwig, Marx, Hill and Browning, 1969	CS	1	31	Schizophrenia, assaultive	Hot Shot Sabre Six	"pseudocatatonic sit down" (muscular freezing or melting), lesser aggressive action, self-aggression, aggression fantasies, surrogate retaliation, threats, warnings. No tissue damage or other adverse physical effects.
Merbaum, 1973	CR	1	12	Autism, SIB	Shock stick	Cry of pain and immediate fear of the shock device
Miron, 1971	CS	11	NS	NS	NS	Possibility of symptoms substitution
Mudford, Boundy and Murray, 1996	CR	1	36	MR, SIB	TSD, Hot Shot Sabre Six (HSSS)	• TSD, Slight local tremor in the thigh • HSSS, Arc burns to the skin, grimacing, flinching, vocalizations indicating pain or annoyance
Muttar et al., 1975	CR	1	10	DD, SIB	NS	No adverse side effects, such as disruption of social relationships, were noted
Prochaska et al., 1975	CR	1	9	MR, seizures	A Farrall A-V-2 shocker 2 mA pulsating 0.5 s	Symptoms substitution, head-snapping (which was then successfully treated).
Ricketts and Goza, 1993	CR	1	28	MR, SIB, epilepsy	**SIBIS**	• Lesion (bruise) on skin, the shape of an electrode, resolved in 1 week. • Development of episodic bursts of SIB, aggression toward others.

Reference	Study Type[1]	Number of Subjects	Age[2] (years)	Diagnoses[3]	Device[4]	Reported Adverse Events
Salvy et al., 2004	CR	1	3	Partial trisomy 2; DD	**SIBIS**	No negative side effects observed
Simmons and Reed, 1969	CR	1	5	MR, SIB	NS	No evidence of development of fear
Baroff and Tate, 1968	CR	1	9	Blind, autism, SIB	Stock prod (Sears & Roebuck #325971) 130 V	Phobic response to buzzing sounds
Van Oorsouw et al., 2008	CS	9	8-30	SIB, aggressive behavior	**GED-1**	Crying, making whining noises, spitting, stamping feet, smearing feces, screaming, swearing, making obscene gestures, shrugging shoulders, uttering racial comments, making negative facial expressions (e.g., rolling eyes), and imitating others.
Williams, Kirkpatrick-Sanchez, and Crocker, 1994	CR	1	22	MR, SIB, autism	**SIBIS**	Malfunction on two occasions (failed to deliver shock), perspiration and slightly reddened areas
Young and Wincze, 1975	CR	1	21	MR, SIB	Lehigh Valley Electronics	Crying increased

[1] CR, case report; CS, case series, RA, retrospective analysis; CC=Case control.

[2] NS, not specified.

[3] MR, mentally retarded; SIB, serious injurious behavior; SRBP, serve resistant behavior problems; CP, cerebral palsy; DD, developmentally disabled.

[6] NS, not specified; TSD, therapeutic shock device. Note that only the devices, as specified in Section 3.2, have been cleared by the FDA (e.g., SIBIS and GED-1 (same as GED)).

[4] Measure HR as an endpoint.

Several articles examining the use of ESDs for aversive conditioning for other indications were also identified and examined for adverse events. One article (Kenny, Solyom, and Solyom, 1973) reported on a within subjects comparison of baseline compared to treatment with a shock in five subjects with obsessions and compulsions. Anxiety and psychotic delusions reported in one subject. Michaelsson (1976) performed a case control study (12 subjects and 24 controls) using an ESD device to treat alcohol dependence. The author states that symptoms of experimental repression, like headaches, restlessness, and mild dysphoria were common and appeared usually within 3 or 4 days of the treatment. Russell (1970) performed a prospective study of 14 subjects to stop smoking and the author reported that aggression toward cigarettes and mild transient depression were reported in 7 subjects. In another prospective study on 12 subjects using an ESD on alcoholics reported stated that subjects reported discomfort from the shocks. The other identified articles did not report any adverse events but it is unclear whether no adverse events occurred or whether adverse events were not tracked or reported. These included studies using ESDs for alcoholism (Ewing, 1984; Finn et al., 2001; Jackson and Smith, 1978; Smith et al., 1997; Wilson

and Tracey, 1976; and Davidson, 1974) , trichotillomania (Crawford, 1988), weight loss (Johnson and Karkut, 1996), compulsive eating (Wijsinghe, 1973), smoking (Knott and De Lugt, 1991), cerebral palsy (Sachs and Mayhill, 1971), and for inappropriate sexual behavior after traumatic brain injury (Jan ter Mors et al., 2012).

In addition to publications with specific information regarding AEs, twelve reviews (containing no new clinical information) examining AEs associated with aversive conditioning in general or aversive conditioning using ESDs were identified. These included:

- Azrin and Holz, 1966
- Balsam and Bondy, 1983
- Bachman, 1972
- Berkowitz, 1983
- Butterfield, 1975
- Carr and Lovaas, 1981
- Corbett, 1975
- Craven, 1970
- Lernan and Vorndran, 2002
- Lichstein and Schreibman, 1976
- Logan and Turnage, 1975
- Meyers and Evans, 1989

Balsam and Bondy (1983) conducted a literature review of the negative effects of aversive conditioning devices in general (i.e., not specific to ESD). Operating within a primarily behavioral conceptual model, they note numerous potential adverse events including, emotionality/aggression, general behavior suppression, inflexible responses, escape, avoidance, aggression, generalization, specificity, correct responses not taught and negative modeling.

Lichstein and Schreibman (1976) conducted a literature review specifically examining reports of using ESDs in autistic children (See Figure 4 below). They identified 12 articles and noted positive as well as negative effects of treatment. Eight articles reported positive effects while seven articles reported negative effects. Five articles reported both positive and negative effects. Positive effects were discussed previously in Section 5.1.2. Negative side effects included, fear, quiet, sullenness, aggression, crying, shivering, decrease in happiness-contentment, dependency, substitute SIB, aversion to treater/device.

Positive and Negative Side Effects of Electric Shock on Autistic Children Reported in 10 Studies

Study	Side effects	
	Positive	Negative
Baroff and Tate (1968)		1. fear of buzzing sounds (+)[a]
Birnbrauer (1968)	1. sociability (+) 2. cooperation (+)	
Bucher and King (1971)		1. fear of shock device (+) 2. quietness (+) 3. sullenness (+)
Bucher and Lovaas (1968)	1. eye-to-face contact (+) 2. imitation skills (+)	1. aggression (+) 2. crying (+) 3. shivering (+)
Lovaas et al. (1965)	1. alertness (+) 2. affection (+) 3. sociability (+) 4. happiness (+) 5. pathological behaviors (−) 6. affection-seeking behaviors (+)	1. happiness–contentment (−)[b] 2. dependency (+)
Lovaas and Simmons (1969)	1. avoiding social contacts (−) 2. whining (−)	
Merbaum (1973)	1. sociability (+) 2. quietness (+) 3. happiness (+)	1. fear of shock device (+)
Risley (1968)	1. eye contact (+)	1. chair climbing (+)
Simmons and Lovaas (1969)	1. affection (+) 2. eye contact (+) 3. smiling (+) 4. hugging (+)	1. temporary aversion to experimenter (+) 2. aversion to shock stick (+)
Tate and Baroff (1966)	1. calmness (+) 2. smiling (+) 3. sociability (+) 4. playfulness (+) 5. whining and crying (−)	

[a] The + denotes an increase in the behavior.
[b] The − denotes a decrease in the behavior.

Figure 4: Positive and Negative Side Effects of Electric Shock on Autistic Children Reported in 10 Studies (Lichstein and Schreibman, 1975, p. 169)

Some reviews note that when shock devices are not designed and applied appropriately adverse consequences such as burns, tissue and nerve injury, cardiac arrhythmias, respiratory failure and even death if electrodes are placed transthoracically. The more serious potential adverse events appear to be correlated with higher intensities of electrical stimulation (e.g., greater than 100 mA through the heart) (Craven, 1970, Butterfield, 1975, Logan and Turnage, 1975). However, no reports of nerve injury, cardiac arrhythmias, respiratory failure or death have been reported in the literature for use of ESDs for aversive conditioning. Most studies which identify a current for aversive conditioning have reported using about 5 mA and it is recommended that electrode pairs be placed on a single limb to avoid risks associated with stimulation of the heart (Butterfield, 1975).

Most of the reviews acknowledge the possibility of negative emotional reactions such as, fear, avoidance, aversion, anxiety and depression (Balsam and Bondy, 1983, Tanner, 1973, Logan and Turnage, Corbett, 1975, Lichstein and Schreibman 1976, Meyers and Evans, 1989, Lernan and Vorndran, 2002). The other group of possible adverse events noted in some reviews included retaliation, increased aggression, or substitution of one injurious behavior for another (Balsam and Bondy, 1983, Lichstein and Schreibman, 1976, Berkowitz, 1983, Meyers and Evans, 1989, Lernan and Vorndran, 2002). Two reviews concluded that ESDs for aversive conditioning is not associated with any significant adverse events (Carr and Lovaas, 1981, Bachman, 1973). Moreover, Lichstein and Schreibman (1976) contend that physical discomfort and emotional reactions are required in order for the treatment to be effective. Therefore, they argue that these effects may be considered indicators of the main effects of treatment rather than unwanted side effects.

In summary, AEs from the case series/reports as well as the case control study and retrospective review were categorized into the following categories:

- Anxiety (6 reports)
- Fear and aversion/avoidance (6 reports)
- Substitution of other negative behaviors (5 reports)
- Burns and other tissue damage (4 reports)
- Depression/crying (4 reports)
- Pain/discomfort (3 reports)
- Neurological symptoms (1 report)
- Malfunction (1 report)
- Other negative emotional reactions or behaviors (11 reports)

This list of AEs identified in the published literature in absolute terms may appear to be relatively modest in terms of severity and frequency of occurrence. However, it is important to note that the literature suffers from a number of limitations. As stated in the review of benefits, there has been virtually no systematic investigation of ESDs for aversive conditioning for SIB and/or aggressive behavior and by various reports; only a very small number of patients are subject to its clinical use. The bulk of articles identified in the searches have been case reports/series employing retrospective review of clinical information. In addition, the majority of the articles were published over 40 years ago, and as such did not adhere to current research or reporting standards. Particularly with regard to

AE's associated with ESD use, no articles described employing a systematic assessment of AE's and many did not state if attempts were made to assess AEs or not. Any attempts to assess AEs (particularly psychological AEs) may also have been hindered due to the difficulty of some subjects (i.e., intellectually disabled) to report such effects.

For the reports of AEs that do exist, many were published during a time when conceptions of disease and pathophysiology (particularly psychiatric pathophysiology) differed significantly from our current understanding. As a result, pathological processes may have been interpreted from a different perspective, certain currently accepted disease processes (e.g., acute and post-traumatic stress) may not have been recognized, and certain symptoms/AEs may not have been accurately identified/reported.

It is also important to consider the possibility of bias against reporting AEs. As previously noted, the majority of articles (all but 3) did not define a systematic method for assessing AEs. In a review by Carr and Lovaas (1981), they concluded that there was no evidence of adverse events associated with ESDs for aversive conditioning. However they went on to opine, "in light of the intrusive nature of shock treatment, it is puzzling that so few negative side effects have been reported. In interpreting the existing literature, we might be wise to consider the possibility that some investigators have been predisposed to see only the positive side effects."

Potential bias against adverse event reporting might also be present in the article presenting a retrospective review of the largest group of individuals (60) receiving ESD for aversive conditioning. The review noted only one negative side effect "temporary discoloration of the skin that cleared up in a few minutes or days." (Israel et al., 2008) However, "temporary emotional behaviors, a temporary tensing of the body, or attempts to remove the device or grab the transmitter noted during treatment were classified as 'immediate collateral behavior' and were not considered adverse events" (Israel et al., 2008). Moreover, in 66 patient case histories submitted by the same group to FDA, no AEs across all patients were reported and no systematic methods for short-term or long-term AE monitoring were defined.

Therefore, while the systematic literature review represents the most rigorous evaluation of risk of AEs associated with ESDs, these results should be interpreted cautiously, and in the context of other information.

5.2 Risks Identified through CDRH's Manufacturer and User Facility Device Experience (MAUDE) Database for Medical Devices

The MAUDE database is maintained by the Office of Surveillance and Biometrics (OSB) in CDRH at FDA. This database contains adverse events and reportable product problems with medical devices. The database was fully implemented in August 1996, and contains individual adverse event reports submitted by manufacturers, user facilities, importers, and voluntary reporters. Medical device manufacturers are required to report known adverse events as part of the general controls that most medical devices are subject to; patients and consumers are also encouraged to voluntarily report AEs.

Over the entire period the database has been maintained, there has been only one report of an AE for the Aversive Conditioning Devices which are designated under the FDA product code HCB. This report was submitted on in 1995 from an unnamed source. It describes an incident of an inadvertent deployment of a "GED device" (an ESD for aversive conditioning) with resulting skin lesions, including "2 ring-shaped marks" and 3 areas of "rough skin".

5.3 Additional Available Information Regarding Benefits and Risks

As noted above, the statute and regulations require FDA to consider "all available data and information" in making a banning determination.[22] Therefore, in addition to the systematic review of the literature for benefits and risks of ESDs for aversive conditioning, other sources of information were reviewed and are summarized in the following sections.

5.3.1 Council on Scientific Affairs, American Medical Association (AMA) Council Report, Aversion Therapy[23]

In 1987, the Council on Scientific Affairs of the AMA provided recommendations for the use of aversion therapy for various indications. They noted that aversion therapy is a series of techniques designed to reduce unwanted or dangerous behaviors and positive reports suffered from a lack of control groups and control procedures. At that time, they concluded that the best accepted application was for the treatment of chronic self-injurious behavior. The council did not limit their consideration of aversive techniques to electric shock, but did conclude that "when behavior is dangerous and has not improved with less intrusive procedures, increasingly aversive techniques, up to electric shock for the most severe, are appropriate."[24] The council also emphasized that the literature for all indications is founded on single or group case studies. Finally, FDA could not find a more recent update of these recommendations.

5.3.2 National Institutes of Health (NIH) Consensus Development Conference Statement, Treatment of Destructive Behaviors in Persons with Developmental Disabilities (September 11-13, 1989)[25]

In 1989, NIH held a conference to review the treatment of destructive behaviors in persons with developmental disabilities. Based on the conference proceedings, consensus recommendations were made for behavior enhancement and reduction approaches. The conference did not specifically consider ESDs for aversive conditioning, though they noted they might be considered behavior reduction techniques. Behavior reduction treatments discussed included, brief (fraction of a second) faradic shock delivered to the skin; a disagreeable tasting substance placed in the subject's mouth; mouth washing; oral hygiene; air, water mist, or ammonia salts placed briefly under a person's nose; or tickling.

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[22]   21 U.S.C. § 360f(a); 21 CFR § 895.21(a)(3)

[23]   Aversion Therapy, Council on Scientific Affairs. (1987). *JAMA*, 258(18), 2562-2566.

[24]   Id. at 2565.

[25]   Treatment of Destructive Behaviors in Persons with Developmental Disabilities. NIH Consensus Statement Online 1989 Sep 11-13, 1989; 7(9), 1-15. (http.//consensus.nih.gov/1989/1989DestructiveBehaviorsDevelopment075html.htm)

The conference reached consensus that behavior reduction interventions appeared to be effective in some individuals, particularly in suppressing destructive behaviors, particularly self-injurious behavior (SIB). The consensus statement states that a majority of the studies of behavioral reduction interventions, maximum (≥90 percent) suppression effects were seen in 1 to 10 days. For the most part, follow-up studies of subjects treated with behavior reduction approaches have revealed that the suppression effect can endure for months and, indeed, persist for up to 2 years after the intervention has been discontinued. The extent to which other environmental factors contribute to this durable change is unclear.

The consensus statement indicated that negative side effects of behavioral interventions also have been reported anecdotally for both behavior enhancement and behavior reduction approaches. For example, some interventions have been found to lead to the emergence of other forms of self-injury or other forms of undesirable behavior. In addition, relapse following discontinuation of treatment may lead to more severe or more intractable forms of destructive behavior. Additional side effects that have been reported include decreased social behavior, increased aggression, and increased stereotypies. Less visible side effects associated with behavior reduction approaches include the potential for abuse in the application of these procedures, the psychological effects on staff, and, most important, the negative and demeaning social image that the use of some of these procedures conveys to the general public about persons with developmental disabilities.

The conference further recommended behavior reduction procedures should be selected for their rapid effectiveness only if the exigencies of the clinical situation require short-term use of such restrictive interventions and only after appropriate review and informed consent are obtained. It is recognized, however, that behavior reduction procedures make little or no direct contribution to providing constructive alternatives to the destructive behaviors targeted for elimination. Thus, the interventions should be used only if they are incorporated in the context of a comprehensive and individualized behavior enhancement treatment package.

Finally, it was noted a major controversy had erupted in the last decade (i.e., the 1980s) regarding the use of behavior reduction approaches (also called aversive treatments). The controversy included both the credibility of the scientific evidence regarding the effectiveness of such techniques and the ethical aspects, legal issues, and social acceptability of these procedures. The consensus statement called for further research on all types of treatment for destructive behaviors in persons with developmental disabilities.

The online report includes the following qualifying statement, "This statement is more than five years old and is provided solely for historical purposes. Due to the cumulative nature of medical research, new knowledge has inevitably accumulated in this subject area in the time since the statement was initially prepared. Thus some of the material is likely to be out of date, and at worst simply wrong."

5.3.3 New York State Education Department (NYSED) Report (June 6, 2006)[26]

The NYSED conducted site visits in April-May 2006 to the Judge Rotenberg Center (JRC) (formerly known as the Behavior Research Institute), a private residential school located in Canton, Massachusetts. The NYSED was sending students with autism, mental retardation, emotional disturbance and multiple disabilities to the JRC at the time of the report. The school serves students who exhibit serious behaviors that interfere with learning and provides an intensive behavioral treatment program to students 24 hours a day, seven days a week. Concerns about the aversive conditioning regimen from a previous site visit as well as questions from legislators and the Board of Regents (NY) prompted investigation by the New York State Education Department in 2006, and an independent report was commissioned. For this report, a sample of 12 New York State students were selected for review from the 71 state students receiving aversive interventions that included electric skin shock, food contingent programs and/or manual or mechanical restraints (Level III Behavioral Interventions).   While the report evaluated all aspects of the JRC program, it focused on health and safety issues related to the use of ESD's for aversive conditioning. The following is a brief summary of the findings with respect to ESDs for aversive conditioning.

The report noted on pages 6-7 that "the most common Level III aversive procedure used at JRC is skin shock in which one or more electrical stimulations are administered to a student after he or she engages in a targeted behavior. Skin shocks are delivered through a graduated electronic decelerator (GED) device (described in Section 3.2 of this Executive Summary). Electrodes were worn by the student on various parts of the body, notably the arms, legs and stomach area, and ranged in number and placement dependent upon the students' behavior program guidelines." Of the NY students at JRC, 53 were receiving stimulation with a GED and 24 were receiving stimulation from a "GED-4" device which is not FDA approved or cleared but has been reported to have a peak output current that is three times that of the FDA cleared "GED". Specifically, the report concluded that the use of the electric skin shock conditioning devices at JRC raised health and safety concerns, and that the collateral effects (e.g., increased fear, anxiety or aggression) on students resulting from JRC's punishment model were not adequately assessed, monitored or addressed.

The report also describes that aversive behavioral interventions are administered "to students with a broad range of disabilities, many without a clear history of self-injurious behaviors" and "for behaviors that are not aggressive, health *[sic]* dangerous or destructive." The report further notes that "there is limited evidence of comprehensive functional behavioral assessments (FBAs)" and "limited evidence of the collection of data relevant to FBAs.   In addition, the report mentioned a dependence on punishment without regard to the type of disability or emotional problem, and mentioned a lack of effort to switch to less restrictive treatments as the condition

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[26]   The complete report can be accessed at, http, //boston.com/news/daily/15/school_report.pdf

improves. The report also mentioned a general use of interventions for behaviors that are not dangerous or destructive. Social interaction, academic instruction and respect for the patients' dignity were all found to be insufficient. The report also found substantial risks of malnourishment, skin burns from the device, and psychological side effects such as fear, aggression, and anxiety, which are not assessed, monitored, or addressed by JRC. Although these adverse events are associated with the overall use of aversive interventions, electric skin shock using the GED was the most common Level III aversive procedure used at JRC. Finally, the qualifications of the personnel were found to be insufficient, as most staff members have only a high school education. The report noted a lack of evidence for monitoring for potential collateral negative effects, such as depression or anxiety, post-traumatic stress disorder (PTSD), or social withdrawal. One student interviewed stated that she had been burned by the GED-4 device while taking a shower. Another student reported feeling "depressed and fearful…desire to kill herself…thought about killing herself every day." (The report did not specify if this was a direct effect of ESDs for aversive conditioning.)

5.3.4 Massachusetts Department of Developmental Services (DDS) Proposed Amendment to Behavior Modification Regulations (Including ESDs for Aversive Conditioning)

On or about June 8, 2011, the Massachusetts DDS published a proposed amendment to its existing behavior modifications regulations at 115 CMR 5.14 to prohibit the use of Level III Behavioral Interventions (including ESDs for Aversive Conditioning).[27] The proposed amendment would not interfere with court-approved treatment plans for individuals who were receiving such aversive interventions nor would it require they obtain any additional approvals, documentation, etcetera, that was currently required under Department regulations. Pursuant to the provisions of Massachusetts General Law Chapter 30A, the DDS held public hearings on July 20, 2011 and July 22, 2011 to take testimony and receive public comment on the proposed regulations. Transcripts of these hearings are publically available.

5.3.4.1 Public Hearing on Aversive Amendment (July 20-21, 2011)

Over two days there were 97 total oral comments, 59 of which came from JRC employees supporting the continued use of ESDs for aversive conditioning for

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[27] Massachusetts Department of Developmental Services (DDS) Regulations 115CMR 514(d),

   (d) Level III Interventions.

   1. Any Intervention which involves the contingent application of physical contact aversive stimuli such as spanking, slapping, hitting or contingent skin shock.
   2. Time Out wherein an individual is placed in a room alone for a period of time exceeding 15 minutes.
   3. Any Intervention not listed in 115 CMR 5.14 as a Level I or Level II Intervention which is highly intrusive and/or highly restrictive of freedom of movement.
   4. Any Intervention which alone, in combination with other Interventions, or as a result of multiple applications of the same Intervention poses a significant risk of physical or psychological harm to the individual

SIB refractory to other treatments. Also included were comments from 7 parents of students, and one past student supporting continued device use. A lesser number of comments were made in opposition to the use of ESD for aversive conditioning, including Senator (MA) Brian Joyce who reported that experts in the field (Ivar Lovaas (professor of neuroscience at UCLA) and Ronald Comer (professor at Princeton University Department of Psychology)) stated that the treatment is not effective long-term. Adverse events such as burns, emotional distress, fear anxiety, and agitation were reported by some speakers. These comments were incorporated and addressed in the DDS commissioner report of October 14, 2011 discussed below in Section 5.3.3.2.

5.3.4.2 DDS Response to Public Testimony (7/20 – 7/21/2011) and Written Comments (10/14/11)[28]

DDS Commissioner Elin Howe wrote a report responding to the public written and oral testimony, as well as a review of the research, opinions of subject matter experts, and positions taken by various organizations and associations. The report concluded the current standard of care for individuals with intellectual disability with the most severe behavioral challenges is positive behavior intervention and does not include aversive interventions or punishment. It was noted that there has been an evolution in the treatment of severe behavioral disturbances in persons with intellectual disability over the past 30 years, and particularly in the last two decades, which has moved towards forms of treatment that are non-aversive and involve positive behavioral supports.   As a result, DDS published the proposed amendment to prohibit the use of Level III Behavioral Interventions (including ESDs for aversive conditioning). As a result, DDS published the proposed amendment to prohibit the use of Level III Behavioral Interventions (including ESDs for aversive conditioning).

The opinion was based both on the body of empirical evidence showing the effectiveness of other less intrusive forms of treatment that do not involve pain; on the overwhelming support of this position by virtually every local, statewide or national organization supporting individuals with intellectual disability, and by providers and clinicians whose practice demonstrates that non-aversive treatment can modify difficult or dangerous behaviors effectively and for the long-term, while aversive interventions, in addition to causing pain and anxiety in such individuals, have no proven long-term efficacy.

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[28] The complete report can be found at http, //www.mass.gov/eohhs/docs/dmr/regs/reg-115cmr514-comments.pdf. Written comments from the following groups can also be accessed on the internet, American Network of Community Options and Resources (ANCOR) (http, //www.ancor.org/ancor-position-statement-behavioral-intervention), National Council on Disability (http, //www.ncd.gov/publications/2011/July182011), and TASH (http, //tash.org/wp-content/uploads/2011/07/TASH-Letter-to-Massachusetts-DDS.pdf)

The report stated that a review of the other 49 states (not including Massachusetts) and the District of Columbia indicates that 21 states specifically "ban" or prohibit aversive interventions through statues, regulation or policy, Alabama, Arizona, Arkansas, Colorado, Connecticut, District of Columbia, Florida, Illinois, Indiana, Maryland, Michigan, Missouri, Montana, Nevada, New Mexico, Oklahoma, Pennsylvania, Rhode Island, South Dakota, Vermont and Washington.

5.3.5 Complaints Made to Massachusetts Disabled Persons Protection Committee

FDA reviewed complaints regarding ESD use for aversive conditioning made to the Massachusetts Disabled Persons Protection Committee (DPPC) from August 30, 1993 to July 28, 2013. Of 53 complaints, 18 were screened out by the DPPC as not meeting complaint criteria and 22 were found to be unsubstantiated. The remainder (some with multiple AEs reported) included,

- Burns/tissue injury – 6 reports
- Inappropriate device use – 3 reports
- Negative emotional reactions – 3 reports
- PTSD - 1 report

5.3.6 Reviews, Letters, and Reports Submitted to FDA from Other Sources

The FDA received reviews and reports from several sources (2010-2013). This information is summarized below,

5.3.6.1 FDA Meetings with the National Council on Disability (NCD), Disability Rights International (DRI), the National Disability Rights Network (NDRN), and the Arc (March 22, 2013), and with the National Leadership Consortium on Developmental Disabilities (NLCDD) (April 16, 2013)

The National Council on Disability requested a meeting with FDA to discuss FDA's role in assessing the use of aversive devices by the JRC and provide related information based on the work NCD has conducted on issues affecting people with disabilities. On March 22, 2013, representatives from NCD, DRI, NDRN and the Arc met with representatives from FDA's Office of the Chief Counsel and CDRH's Office of the Center Director and Office of Compliance. These groups expressed concerns regarding the harmful physical and psychological effects they believe the GED devices have on the patients at JRC, which they believe to be underreported due to the impact these patients' disabilities have on their ability to communicate.

Representatives of the NLCDD requested a meeting with CDRH to discuss ESDs for Aversive Conditioning as used at the JRC. This meeting took place on April 16, 2013. Prior to the meeting, NLCDD provided written information to FDA (March 26, 2010). NLCDD representatives indicated that the GED in

use at the JRC is modified from the FDA cleared GED device and that use has expanded from the cleared indication. They reported that the GED-4 has greater "peak" current than the GED and that repeated applications of the device over a short period of time are administered by JRC, which may increase the occurrence of adverse events, such as burns.

At the FDA meeting held on April 16, 2013, the NLCDD reported the following:

- ESDs for Aversive Conditioning are banned in most states;
- They are aware of at least 4 case reports of psychological trauma and PTSD symptoms; and
- Alternative treatments (positive environmental and reinforcement strategies) have been developed and are currently effective for severe and refractory self- injury.

5.3.6.2   Letter to Margaret Hamburg regarding JRC (February 12, 2013)[29]

Representatives of the disability and human rights community sent a letter dated February 12, 2013 to FDA Commissioner Margaret Hamburg regarding the use of contingent electric shock and other aversive interventions. Among other things, the letter stated that ESDs for use in behavior modification are inherently unsafe and that there are other demonstrated alternative treatments for the patient populations being treated with these devices.

5.3.6.3   Mental Disability Rights International (MDRI) Report, Torture not Treatment, Electric Shock and Long-Term Restraint in the United States on Children and Adults with Disabilities at the Judge Rotenberg Center (2010)

In 2010, MDRI, an international human rights group, published a report regarding what they believed to be the human rights abuses of children and young adults with mental disabilities residing at a facility that employs ESDs for aversive conditioning (JRC in Canton, Massachusetts).[30] The report was an urgent appeal to the United Nations Special Rapporteur on Torture or other Cruel, Inhuman or Degrading Treatment or Punishment; it requested that the Special Rapporteur initiate an inquiry into the abusive practices perpetrated against the residents of JRC and licensed by the State of Massachusetts**.** MDRI contended that "the severe pain and suffering perpetrated against children and adults with disabilities at JRC violates the UN Convention against Torture."

In the report, they provide information on the risks associated with use of the GED for aversive conditioning at the JRC:

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[29] http, //autisticadvocacy.org/2013/02/letter-to-food-and-drug-administration-on-the-judge-rotenberg-center/
[30]   The complete report can be accessed at, http, //www.disabilityrightsintl.org/wordpress/wp-content/uploads/USReportandUrgentAppeal.pdf

- Facility employees reported the level of pain experienced is significant;
- Facility employees noted the occurrence of tremor, burns and tissue injury;
- Facilities employees noted fear, and other negative emotional and behavioral reactions;
- An independent report raised the potential risk of psychological trauma, marginalization, or alienation; and
- The mother of a patient witnessed pain, fear, negative emotional reactions in individuals receiving the treatment.

The UN Special Rapporteur on Torture wrote a letter dated June 11, 2012 to the United States Department of State concerning "the treatment suffered by children and young adults enrolled in the residential program of the Judge Rotenberg Center (JRC)." The US Department of State responded that legislative measures in Massachusetts "will lead to the eventual prohibition of aversive therapy practices in Massachusetts", and New York has indicated that "by June of 2014 all [New York] residents at JRC, including those few who remain subject to court-approved aversive interventions, will be offered placements in New York state where such interventions are not authorized"[31] JRC's Executive Director and GED developer, Matthew Israel, PhD, responded to MDRI's report for JRC. The JRC report concludes that "behavioral skin shock saves individuals with severe behavior disorders from a life of seclusion, restraint and/or warehousing, as well as the ravages of psychotropic medication"[32] A follow-up investigation was initiated by a second UN Special Rapporteur on Torture in 2012. The report called for an absolute ban on "all coercive and non-consensual measures", including "electroshock procedures".[33] In an addendum, the Special Rapporteur determined that the rights of the students of the JRC subjected to Level III Aversive Interventions by means of electric shock and physical means of restraints have been violated under the UN Convention against Torture.[34]

5.3.7 Data Obtained by the FDA/CDRH/Office of Compliance (OC) regarding the use of ESDs at JRC

5.3.7.1 Use of Unapproved Devices at JRC
In 2011, FDA determined that the GED devices currently in use at JRC have been modified from the GED device that FDA cleared in 1994 such that a new clearance or approval is required, which JRC has not obtained. As a result, these devices are adulterated under the FD&C Act, which FDA explained to JRC in an "Untitled Letter" dated May 23, 2011. On October 3, 2012, through October 17, 2012, an investigator from FDA inspected the JRC facility located

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31 https, //spdb.ohchr.org/hrdb/22nd/USA_02.01.13_(6.2012).pdf
32 http, //dotnet.judgerc.org/Documents/judgercdocs/EmailtoMinton.pdf
33 http, //www.ohchr.org/Documents/HRBodies/HRCouncil/RegularSession/Session22/A.HRC.22.53_English.pdf).
34 http, //www.ohchr.org/Documents/HRBodies/HRCouncil/RegularSession/Session22/A-HRC-22-53-Add4_EFS.pdf

at 250 Turnpike Street, Canton, Massachusetts, and observed an inventory of the GED-3A and GED-4 devices at the facility. FDA determined neither of these GED devices have the required marketing clearance or approval. As a result, the FDA issued a Warning Letter to JRC dated December 6, 2012.[35] In connection with this compliance investigation of JRC, JRC provided documentation regarding use of its GED devices to FDA (discussed further below).

5.3.7.2 Patient Case Summaries

JRC provided FDA the following information during the first quarter of 2013 for the students at JRC who are receiving aversive conditioning with ESDs. This data was requested as part of the ongoing compliance investigation and as additional information for the health risk assessment. These patient files included:

- Court findings, orders and approved treatment plans with the GED device;
- Medical and treatment records from prior to and during admission at JRC;
- A recent medical report by a physician addressing the current status of the students' need for treatment with the GED device;
- Evaluations of each student by State-appointed independent experts in psychology addressing the students' need for continued access to the GED device; and
- Comprehensive treatment summaries for each student.

The records indicate that as of February 8, 2013, 86 students had court-approved treatment with the GED device. Of these, 66 students had treatment plans that included the use of the GED device. Many patients have been treated with the GED-4, which has an average current that is almost three times that of the FDA cleared GED device (Israel et al., 2008). FDA reviewed the records, which are summarized in Appendix I with all patient identifiers removed. The age range of patients being treated at the time the records were reviewed was between 14 and 50 years (Mean: 30.2 ± 11.5 years) and there were 72 males and 18 females. Treatment duration was difficult to determine as only the admission date to JRC was provided in these case histories. Diagnoses included various levels of mental retardation, severe behavior disorder, autism, pervasive developmental disorder, seizure disorder, attention deficit hyperactivity disorder, and a variety of medical disorders (e.g., Angelman's syndrome). The target behaviors for the GED primarily involved SIB/aggression but also included physical and sexual assaultive behavior, pica, and destructive behavior. According to the records, no adverse events were reported for any of the patients.

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[35] A copy of this warning letter can be found at, http, //www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm331291.htm.

5.3.7.3   GED Complaint Files

In follow-up to FDA's Untitled Letter dated May 23, 2011, JRC sent FDA monthly status updates. JRC performed a retrospective review of all GED complaints since 2009 and provided this information to FDA in its November 5, 2011, status update letter. This retrospective review encompassed 1,830 "Forms," which are used by JRC staff only, and serve purposes other than for complaint reporting. Though some of these reported device malfunctions, and many were missing information, there was only one reported injury, a burn mark on the arm of patient where an electrode had been. JRC determined that the GED could not have caused this injury because the patient had not received any GED applications in the previous seven days. JRC stated that, "A medical assessment was performed, noting that the 'client had sustained what appeared to be a second degree burn on the left inner side of his arm, the size of a dime. It seemed to be a new mark, the wound was pink and some serous (thin, watery) drainage was noted. First aid was applied.' On June 28, 2010, it was further noted that 'the left upper arm wound was currently healing.'

5.3.7.4   JRC Policy Document, "Procedures to Facilitate the Assessment of Possible Collateral Effects"

In a document with the heading "JRC Policy," entitled, "Procedures to Facilitate the Assessment of Possible Collateral Effects (Revised Date, 6/14/2012)," there is an acknowledgement that "the use of Level III aversive procedures may produce some negative side effects and JRC staff should be aware of these. JRC staff must be vigilant in assessing whether aversive interventions are causing any short-term or long-term collateral effects, such as increases in aggression, escape behaviors, emotional reactions, sleep difficulties and any other physical or emotional reaction or change…such changes could include not only immediate, physical observations (such as temporary redness of the skin) but also longer-term, non-physical consequences." (p. 46)

The document distinguishes between two types of risk associated with the used of "GED Level III procedures", physical and psychological/behavioral. "Physical risks associated with skin shock may include temporary skin redness, which clears up within a few minutes or a few days at most, and the extremely rare possibility that a small blister may appear. The psychological/behavioral risks that might be associated with GED Level III procedures include anxiety (nervousness, tensing muscles) during the period between the occurrence of the behavior and the occurrence of the programmed consequence and escape responses." (p. 46)

Staff are instructed to observe for the following "collateral" effects related to the administration of any aversive intervention, not just the GED, Nightmares; Intrusive thoughts; Avoidance behaviors; Marked startle responses; Mistrust; Depression; Flashbacks of panic and rage; Anger; Hyper-vigilance; and Insensitivity to fatigue or pain. Staff are also instructed to observe for any form of distress or discomfort including but not limited to, Changes in sleep patterns;

Loss of appetite; Confusion; Irritability; Lack of energy; Sadness; Mood swings; Significant weight loss; Loss of interest; Fatigue and lack of energy; Difficulty concentrating; Agitation, restlessness, or irritability; Withdrawal from usual activity; and Feeling of helplessness. (p. 48-49)

5.3.8   Clinical Interviews

FDA clinicians have interviewed three individuals who have received ESD administration for aversive conditioning at JRC.

Individual #1
Two FDA clinicians (a neuropsychologist and a psychiatrist) conducted a telephone interview with one of the individuals (March 27, 2014). This individual reported being placed at the JRC residential facility, which used ESD for aversive conditioning on him from the age of 18 to the age of 21 for "violent behavior." He reports that other treatments (negative and positive reinforcement) were attempted for a few months, before ESD was administered. He was placed on the GED-4 device. JRC described the stimulus as being like a "bee sting," but he reported it felt much stronger than that, "like a thousand bees stinging you in the same place for a few seconds." He said the trigger for receiving the stimulus was not only SIB/aggressive behavior, but also for things like noncompliance with staff direction, talking too much and being disruptive in class. The individual did not feel that ESD was effective; it only made him fearful. In terms of AEs, he reported burns that lasted a few days, but no other long-term physical effects. He reported ongoing psychological effects to this day. With the device applied, he described being in constant fear, and not having any idea of when one might be shocked or why. During that time, he experienced a general level of anxiety and fear. Currently (5 years later), he said that he has panicky moments when reminded of the shocks, has a general fear of being controlled, and a dislike of authority. He reported experiencing flashbacks, but denied nightmares. He denied experiencing depression or suicidality.

He also stated that his underlying condition was due to overmedication, and after he left the facility and was taken off all medications, the violent behavior went away. He is currently doing well, is living independently, and going back to school. He stated that ESD use "is torture, in the plainest sense of the word; it's basically administering pain and punishment. If you don't condone spanking, you can't condone this."

Individual #2
The same two FDA clinicians (a neuropsychologist and a psychiatrist) conducted a telephone interview with a second individual (March 27, 2014). This individual suffered from noticeable cognitive disability and the interview was limited by his difficulty with organization and attention. He reported that he was placed at JRC, which employed ESD for aversive conditioning for 9 years and over that period of time received multiple applications of the device. He noted that they tried other treatments (i.e., spanking, finger pinching, and rewards) for about 6 months prior to initiating ESD use. He said he was on the "GED-2" device. "They give you painful shocks," which he described as a "bad bee sting." He reported getting shocks for non-SIB behaviors such

as stealing things, destroying things, swearing, or nagging. He felt the device worked for his behaviors while he was on it, but then didn't work after they took it off. In terms of AEs, he said he got many burns on his skin, but no permanent marks or scars. While he was on the device, he was anxious and afraid that he was going to get shocked. He denied any long-term effects, nightmares, flashbacks, other PTSD symptoms or depression. He is currently at a different residential facility that does not employ ESD and stated that his current treatment is helping to control symptoms as much as any other past treatment he has had.

Individual #3
A third individual was interviewed on two occasions (January 29, 2013; follow up March 20, 2014) by FDA clinicians (neuropsychologist, psychiatrist, and an internal medical physician). This young woman reported a diagnosis of Asperger's syndrome, tics, and repetitive behaviors. She had a long history of SIB. She entered a program at JRC that used ESD for aversive conditioning when she was in her early twenties, and was treated with two types of devices (GED-3A and GED-4) over a 7 year period. As discussed above, the GED-3A and GED-4 are not FDA cleared devices and the GED-4 a much higher output than the cleared GED device. She described the shock as being extremely painful and gauged the pain level of the GED-3A as a 5-8 out of 10 (depending on the location of the shock) and the GED-4 as a 7-8 out of 10. The device was applied to her arms, calves and stomach; later they were changed to her finger tips, bottom of her feet and inner thigh. Staff moved the device electrodes to maximize pain. She noted that she felt she had a high tolerance for pain, and also felt the GED-4 stimulation was not necessarily more painful, but was more "forceful." During that time, she estimated that she received hundreds of shocks. Regarding the administration, she noted that she did not know what behaviors would elicit a shock, and often felt she received shock for no reason. She always felt anxious and on guard. Sometimes if she knew she was going to receive a shock, she would "go after" the person who was going to administer the shock.

In terms of benefit, she feels that the device may have helped some individuals; she described these individuals as "high functioning" and able to stop the targeted behaviors "if they wanted to." But in her case, she did not feel in control of her SIB, with urges that continued to build if they were not relieved. ESD use did decrease the SIB targeted behaviors, but did not address the underlying condition. She said she then found new and secret ways to injure herself. Eventually, she was able to transfer to a different facility that did not use aversive conditioning. She feels that the ESD treatment did not help her and in fact made her worse.

She said that adverse effects of the treatment were never asked about, and she did not receive an appropriate medical examination during her time at the facility. As a result of ESD administration, she reported burns, scars, paresthesia/loss of sensation/numbness, muscle contractions/spasms, pain, heart palpitations, seizure, anxiety, fear, depression, suicidality, nightmares, flashbacks, and re-experiencing symptoms (for example, the sound of Velcro/seeing a wallet being opened causes extreme anxiety)."

On one occasion, after receiving 7 administrations to the leg, she experienced paresthesia and loss of sensation/numbness to the leg. She saw a neurologist after that who suggested a diagnosis of "nerve damage" but did not recommend any further treatment. She notes that the symptoms lasted about 1 year.

She recalled that during her time at the facility (given the overall treatment experience there) she became severely depressed and suicidal, thinking of ways to kill herself. She also notes that she developed PTSD symptoms of startle, hyperarousal, flashbacks and nightmares which continue to the present time. Triggers for her symptoms include discharges of static electricity and the sound of Velcro (which were used to hold the device in place).

Currently, she is at a different residential facility that does not use ESD. She reports feeling and functioning much better with her current treatment. She is functioning well socially and holds a job. She said that ESD for aversive conditioning might seem like it was helpful to someone observing from the outside, but "it's not a life that anyone would want to live."

5.3.9   Reports from Parents of Patients Administered ESDs for Aversive Conditioning

On January 18, 2013, attorneys for the Judge Rotenberg Center Parents Association ("JRCPA" or the "Association") sent a letter to the CDRH Office of Compliance to describe the impact, from a parent's point of view, of eliminating access to GED3A or GED4 from specific patients. Members of the JRCPA share information about the school, much of which is acquired from site visits and their review of JRC's programs, and sit on the JRC Human Rights Committee, which evaluates the programs of clients who have been prescribed treatment with the GED-3A and GED-4 devices. Letters from three parents that express the need for their children to continue receiving GED-3A or GED4 treatment were included as attachments. These letters describe the severe physical harm their children inflicted on themselves and the countless placements and treatments, including cocktails of dangerous medications, they tried to prevent such injury, with no success. They further explain how JRC's treatment program, including GED-3A or GED-4 treatment, was able to stop their children from engaging in dangerous behaviors, allowing them to be free from physical and emotion harm and, for the first time in their lives, to learn and be happy. The letter states that that premature termination of the use of the device will cause great, and in some cases, permanent harm.

JRCPA's attorneys presented case summaries in the letter for three patients treated with the GED-3A and for four patients treated with the GED-4. The following was reported for the three patients receiving the GED-3A:

- This is a patient suffering from Autism and Profound Mental Retardation (PMR). Before and after coming to JRC he engaged in behavior multiple times per day such as banging his ears, slapping his face, hitting his head against hard objects, touching

other clients' genitals, and attacking staff. He was treated at highly reputable facilities prior to JRC and received a wide variety of positive interventions and medications, and was frequently physically restrained. JRC continued to try a range of positive interventions for four months without success. When the GED-3A was added to his program, his dangerous and disruptive behaviors fell from more than four thousand per month to less than two hundred per month. He no longer needed to be restrained dozens of times per month; he was able to make academic progress; his relationship with family improved; and he was able to go on trips in the community. He has been faded to wearing two GED-3A devices and has had a range of behaviors removed from treatment, but so far his self-injurious behaviors have reemerged whenever the remaining devices were temporarily removed.

- This patient suffers from Mild Mental Retardation (MR), Opposition Defiant disorder and a severe behavior disorder. During the first seven years of his life his behaviors included attacking peers, stabbing a child at school with a pencil, sexually touching others in the home, and hitting or kicking teachers. He was placed in at least four treatment facilities, hospitalized on at least two occasions, and prescribed various psychotropic drugs including Lithium and Thorazine. He received speech and language services, structured play therapy, social skills training and counseling, basic token economies and structured schedules, and physical and chemical restraint, all without success. With more sophisticated positive interventions at JRC his behavior slowly improved, but still included hundreds of aggressive, destructive and self-harmful incidents per week. After approximately a year, the GED-3A was added to his program, and his violent, destructive and self-harmful behaviors reduced to less than ten per month. The GED-3A was activated only thirty-two times in the first five years he wore it. The change in his behavior allowed him to receive an education, go on home visits and field trips, and end the need for routine physical restraints. He now wears fewer devices and has fewer behaviors subject to consequences, but every time the device has been entirely removed his aggressive behaviors have swiftly returned.

- This patient suffers from Severe MR and Pervasive Developmental Disorder (PDD). Before and after joining JRC, his behaviors included hitting and biting others, hitting, biting, and head-banging, and picking his skin until it bled and then picking at scabs so they could not heal. When he joined JRC, he was taking seven psychotropic medications, weighed over 300 pounds as a side-effect of his medications, and had to be physically restrained hundreds of times per month. Despite the JRC's program of positive interventions, he continued to engage in thousands of dangerous and disruptive behaviors per month. When the GED-3A was added to his program, those behaviors reduced to less than eighty per month. As a result, he was able to make progress in his education and return to a healthy weight; no longer needed to be physically restrained; no longer picked at scabs enough to prevent healing; and was able to go on community outings and overnight home visits. In his early twenties he was transferred to another institution where GED treatment was not available. He quickly regressed, had to be routinely restrained, resumed medication and became a threat to himself and others. He has

since returned to JRC and resumed treatment with the GED-3A and his behavior has gradually returned to normal.

The following was reported for the four patients receiving the GED-4:

- This patient suffers from PMR, Down's Syndrome and a severe behavior disorder causing her to engage in severe self-injurious behavior. Prior to JRC her attacks on her own eyes, chin and jaw caused cataracts, blindness in her left eye, calloused areas making her eyes appear swollen shut, and many scars on her face. Her previous caretakers, including those at a renowned clinic, tried medications such as Haldol, restrictive environments, in-home behavioral services, and protective helmets all without success. At JRC, prior to adding the GED to her treatment plan she engaged in over five thousand self-injurious behaviors per month. With the GED3a, the need for physical restraint fell from hundreds or thousands per month to zero, but she still engaged in approximately one hundred self-harmful behaviors per month. The GED4 reduced that number to approximately four per month, and the GED is no longer used to control her aggressive and destructive behavior. However, when the GED4 was removed entirely for four days in June 2012, her self-injury jumped back to thirteen incidents per day.

- This subject suffers from SMR, and has been diagnosed with Autistic Disorder and PDD. At his previous placement, his self-injurious behaviors included "body hits to the environment, head hits to wall and floor, body punches, face or head hits, self-bites" and hand contortions, causing bruises, scratches, swelling of joints, cuts to the forehead and fractured bones. His violent behavior sent multiple staff to the emergency room with back and neck injuries and concussions. His positive-only treatments- designed by "internationally-recognized behavior experts" included functional assessments, contingent rewards, teaching functional communication responses, restraint as positive reinforcement, periods of no or high demands, and fulltime staffing. Psychotropic medications including Risperdal, Trileptal and Seroquel were also tried but it could not treat him safely or effectively. At JRC, he received a wide variety of behavioral interventions over eleven months, but continued to engage in approximately five hundred aggressive and health-dangerous behaviors per week. When the GED4 was introduced to his program that number dropped to less than four per week. His time spent in four-point restraints went from approximately ten hours per week to zero; he no longer had to wear a protective helmet; he began making regular educational progress; he was no longer covered with bruises and cuts; and his mother stated that he was "like a new person." It is hoped that the GED4 can eventually be removed entirely, but so far his violent behavior has reemerged whenever it is removed.

- This patient has received a wide variety of diagnoses for her severe aggressive behavior. Her aggression, in which she would often grab others by the hair and kick, scratch, and bite them, caused her to be hospitalized five times in the three years before she came to JRC. She was prescribed twenty-five different medications at various times including Thorazine, Haldol and Lithium. Her therapies at various

specialized day and residential schools included noncontingent reinforcement; differential reinforcement; attention extinction; response blocking; 1, 1 staffing; ORO schedules; allowed escape; reinforcer choice; and level systems. After she came to JRC, the school continued to try its own positive interventions for thirty weeks without success. When the GED3a was added to her program, her dangerous behaviors fell from thousands to hundreds per month. After the GED4 was added, these behaviors fell to less than ten per month, and now often reach zero. She has been able to receive knee surgery to correct injuries from previous mechanical restraint; to make educational progress for the first time; and to go on home visits. Her caretakers are very gradually fading the GED4 and other treatments.

- This patient suffers from PDD and profound MR. His self-injurious behaviors include vomiting and rumination to the point of dangerous weight loss, biting through his tongue and cheeks, and grinding his skin against objects to the point of exposing bone. Given the risks of malnutrition and infection, his behaviors pose a serious threat to his life. Because of the profound and life-threatening nature of his illness, he was placed directly on the GED4 as soon as aversives were added to his program. The effect has been to reduce his aggressive behaviors from hundreds or thousands per month to about two per month. And his health-dangerous behaviors to about forty per month. He has been able to see his family more frequently, feed and dress himself, and has shown more positive affect. When the GED4 has been occasionally removed, his behaviors have immediately returned. If it is withdrawn, he will need to be heavily medicated and restrained to prevent him from destroying his own skin, and his ruminating and vomiting- which cannot be effectively controlled by restraint and medication –will once again become life-threatening.

In summary, the letters and case reports state that there is evidence that the GED-3A or GED-4 device prevents the need for routine physical and mechanical restraint or heavy sedation, protects patients from regular self-inflicted- in some cases life-threatening- injury, and that it allows them to spend time with peers, in the community, and with family. On the risk side, there was no report that the GED-3A or GED-4 caused physical or emotional harm.

5.3.10 Media Reports and Other Public Information

5.3.10.1 Published Reports

In the past several years, several media reports have been published regarding the use of the GED aversive conditioning device at the JRC.[36] Within these reports, there have been claims of device misuse, pain, burns, and physical and psychological consequences, including depression, suicidality and PTSD. At

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[36] New York Magazine "31 Shocks Later" (9/2/13); Forbes "Autism Shock Therapy Practiced in US is Torture, Says UN Official" (2013); MDRI "Torture not treatment" 2010; Boston Magazine "The Shocking Truth" 2008; Jennifer Gonnerman, Nagging? Zap. Swearing? Zap., 32 Mother Jones, 36, 41 (Sept.-Oct. 2007); Mother Jones "School of Shock" (2007); Boston Globe "State checking burn claims at school" 2006; and CNN, report by Anderson Cooper.

least three media reports were supportive of the use of ESDs for aversive conditioning.[37] It is important to note that these media reports are not systematically collected and may be inherently biased sources of information. They include varying levels of clinical expertise and were not peer reviewed for accuracy. Still, they may contain important information about the benefits and risks of device use, and the information is included because the banning criteria require consideration of all available data and information.

5.3.10.2 Report by Monitor Judge Isaac Borenstein (Ret.) on the Judge Rotenberg Education Center (JRC)

Following an incident at JRC on August 26, 2007, in which two students received a significant number of inappropriate GED applications, Dr. Matthew Israel, then Executive Director of JRC, was indicted by a special grand jury on charges of accessory after the fact and misleading an investigator or a witness on May 20, 2011. JRC then entered into a deferred prosecution agreement with the Massachusetts Attorney General that required the appointment of an independent monitor to review and assess safety at JRC in connection with this incident and ensure a similar event would not recur. Judge Isaac Borenstein (Ret.) was retained as the independent monitor, and issued the required report on February 22, 2013[38]. The report explains that the incident was the result of a hoax perpetrated by a prior student, and is not representative of standard practices at JRC. It is included in this review because it reports sequelae of device use.

The incident took place in the early morning hours of August 26, 2007. An individual, later identified as a former student, called into the residence and pretended to be a member of the Quality Control Department of the facility. At the direction of the caller, staff members administered 77 ESD (GED-4) applications to one student and 29 applications to a second student.

According to a medical report and other facility documentation, as a result of these applications, the first student sustained multiple red marks on his lower abdomen. During the application, he began shaking and breathing deeply. Staff observed that his skin was red. The student reported that his mouth was dry, blood pressure racing, he was sweating and he felt like he was about to have a stroke. He reported symptoms of pain, inability to breathe and exhaustion. The second student sustained a "stage II ulcer on his left calf" (according to facility documentation). After the applications, the student reported his leg was "killing" him and asked them to call a nurse.

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[37] The New York Times, "Parents Defend School's Use of Shock Therapy" (12/25/07), "Response to Mother Jones article "School of Shock" (http, //www.judgerc.net/SummResponsetoGonnermanArticle.pdf), and "Torture or Treatment?" (http, //www.psychologytoday.com/blog/radical-behaviorist/201007/torture-or-treatment)

[38] Report is available at http, //autistichoya.files.wordpress.com/2013/05/report-by-monitor-judge-isaac-borenstein-ret-for-the-judge-rotenberg-educational-center-jrc.pdf

The report explicitly does not take a position on the use of GED aversive treatments or make any recommendations on the appropriateness of the use of GEDs at JRC.

5.4   Summary of Available Information

5.4.1   Benefits

The available information on the benefits of ESDs for aversive conditioning to treat SIB and assaultive/destructive behavior associated with developmental disabilities consists of published scientific literature, information provided to FDA, independent reports, information from other public agencies, public hearings, clinical interviews conducted by FDA and other sources of information (legal proceedings and media). The published scientific literature represents the highest quality information available; however, the current literature suffers from the relative lack of scientific investigation conducted on ESDs for aversive conditioning to treat SIB and aggressive behavior; the absence of systematically conducted, well-controlled, prospective investigations; the prominence of retrospective, case study reports; and the variable quality of those reports. In addition, the use of alternative or adjunctive treatments was not well-controlled in these reports. Given the weaknesses of the available information, any conclusions should be cautiously considered.

Letters and case reports, provided by the JRCPA, state that there is evidence that the GED-3A or GED-4 device prevents the need for routine physical and mechanical restraint or heavy sedation, protects patients from regular self-inflicted- in some cases life-threatening- injury, and that it allows them to spend time with peers, in the community, and with family. On the risk side, there was no report that the GED-3A or GED-4 caused physical or emotional harm.

The literature review and other sources of information, including the parent reports above, suggest that short-term (i.e., time period surrounding treatment) benefit is supported, while significant concerns exist about the long-term effectiveness. The analysis also provided some support for magnitude and duration of effectiveness being related to the intensity of the stimulation applied (i.e., lower stimulation is associated with smaller magnitude and shorter duration). Such a conclusion would not completely agree with the NIH consensus statement regarding treatment of destructive behavior (1989), which noted effectiveness of behavioral reduction methods both in the short-term and for up to two years. However, the consensus statement applied to behavior reduction techniques in general, and did not specifically pertain to ESDs for aversive conditioning. The FDA literature review results are similar to that of two noted researchers in the field (Skinner and Lovaas), who also concluded that punishment methods (Skinner) and ESD for aversive conditioning (Lovaas) demonstrate short-term benefit but lack demonstrated long-term durability.

5.4.2   Risks

Similar to the available information for the benefits analysis, the information for the risk analysis consists of published scientific literature, information provided to FDA,

independent reports, information from other public agencies, public hearings, clinical interviews conducted by FDA and other sources of information (media reports and a legal proceeding).   In contrast to the systematic literature review for benefits, the review of risks included articles reporting the use of ESDs for aversive conditioning for several indications. The published scientific literature represents the highest quality information available but, as stated previously, suffers from the relative lack of scientific investigation conducted in this field, the absence of systematically conducted, well-controlled, prospective investigations, the prominence of retrospective case study reports, and the variable quality of those reports. Moreover, particularly related to AE reporting, the published literature suffers from evolving standards of AE reporting (i.e., more recent publications are more likely to present adverse events), with 14 of 33 articles being published before 1980. Of the 34 articles reporting clinical data relevant to AEs data, 6 contained no report of whether subjects experienced AEs (or not), and only 3 reported a systematic method to monitor AE's.

The following AEs were identified in the systematic literature review:

- Anxiety (6 reports)
- Fear and aversion/avoidance (6 reports)
- Substitution of other negative behaviors (5 reports)
- Burns and other tissue damage (4 reports)
- Depression/crying (4 reports)
- Pain/discomfort (3 reports)
- Neurological symptoms (1 report)
- Other negative emotional reactions or behaviors (11 reports)

One device malfunction was reported although it is not known whether this led to an AE. AE associated with ESD treatment for other indications included:

- Anxiety and psychotic delusion
- Headaches, restlessness, mild dysphoria
- Aggression
- Mild transient depression
- Discomfort

Additional concerns about potential AEs came from other available sources of information as well. In contrast to the systematic literature review, information from these other sources may be more susceptible to bias given the lack of peer review, the motivations of the authors, and the circumstances in which the information was presented. Therefore, this information should be cautiously considered. Review of these sources of information identifies the following potential AEs:

- Burns/tissue injury/physical injury
- Fear
- Anxiety

- Aggression
- Trauma/acute stress disorder/post-traumatic stress

Devices malfunctions (e.g., inappropriate and/or multiple stimulations) were also reported but it is unclear whether they led to AEs.

The other sources of information regarding the use of ESDs for aversive conditioning include reference to at least 6 potential cases of post-traumatic stress disorder (PTSD), two instances of depression and suicidality (NYSED, clinical report), and one death. In the cases of the deaths, and in one case of depression and suicidality (NYSED), it is not clear that ESD use was directly associated with the AE. With regard to trauma and the development of PTSD, two of the three individuals interviewed by clinical staff appear to suffer from continued symptoms typically associated with PTSD. There reports support the theoretical perspective that application of a painful stimulus which the individual has not control over may result in acute stress and PTSD symptoms. It is notable, however, that the literature review contained no reports of PTSD. This discrepancy may be explained by the fact that PTSD as a diagnostic category did not start to gain popularity until after its inclusion as a diagnosis in DSM-III (published in 1980). Prior to that time, psychopathology (and symptoms) was understood from different paradigms, including behavioral and psychodynamic theories. Some of the symptom categories identified in the literature review, including fear and aversion/avoidance, anxiety, and depression may be consistent with acute stress/PTSD presentations.

A comprehensive list of potential AEs associated with ESDs for aversive conditioning from all sources includes (in order of number of reports and likelihood, greatest to least):

- Other negative emotional reactions or behaviors
- Burns and other tissue damage
- Anxiety
- Acute stress/PTSD
- Fear and aversion/avoidance
- Pain/discomfort
- Depression (and possible suicidality)
- Substitution of other negative behaviors (including aggression)
- Psychosis
- Neurological symptoms and injury

Some reviews note that when shock devices are not designed and applied appropriately adverse consequences such as tissue and nerve injury, cardiac arrhythmias, respiratory failure and even death can occur if electrodes are placed transthoracically. However, no reports of cardiac arrhythmias, respiratory failure or death have been reported in the literature for use of ESDs for aversive conditioning.

5.4.3 Treatment Resistance

Anecdotal reports may be found of persons who were apparently refractory to all behavioral controls except aversive conditioning ESDs (Israel et al., 2008) along with reports of persons who were successfully treated with less restrictive methods after aversive conditioning ESDs were previously used (Bird and Luiselli, 2000). However, FDA is not aware of any criteria identifying refractory patients or rigorous or systematically collected data that would indicate whether a population exists that is refractory to adequate trials of other available treatment modalities or who are unable to tolerate such treatment modalities due to side effects.

6 Ethical Considerations with Particular Focus on Issues Related to Clinical Studies

This section discusses ethical considerations associated with the use of ESDs for aversive conditioning for the treatment of SIB and aggressive behavior, with a particular focus on issues related to the performance of clinical trials. FDA is required by statute and regulation to consider "all available data and information" in making a banning determination.[39] However, this information is being provided for panel consideration primarily for answering questions related to considerations associated with performing clinical trials using these devices.

Serious concerns have been raised about the use of aversive conditioning ESDs on children and adults with developmental disabilities. As discussed above, in 2010, MDRI published a report appealing to the United Nations Special Rapporteur on Torture to initiate an inquiry into the "abusive practices [of electric shock and long-term restraint] perpetrated against the residents of JRC," contending that "severe pain and suffering perpetrated against children and adults with disabilities at JRC violates the UN Convention against Torture."[40] An investigation was conducted on two separate occasions by UN Special Rapporteurs on Torture. The first investigation resulted in a letter to the United States Department of State concerning "the treatment suffered by children and young adults enrolled in the residential programme of the Judge Rotenberg Center (JRC)." A follow-up investigation resulted in a report calling for an absolute ban on "all coercive and non-consensual measures", including "electroshock procedures" as used at JRC, and an addendum determined that the "rights of the students of the JRC subjected to Level III Aversive Interventions by means of electric shock and physical means of restraints have been violated under the UN Convention against Torture."[41]

A report by the New York State Education Department in 2006[42] that evaluated the behavioral program at JRC concludes among other things that "the use of the electric skin shock conditioning devices as used at JRC raises health and safety concerns" and that "the collateral effects (e.g., increased fear, anxiety or aggression) on students resulting from JRC's punishment

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[39] 21 U.S.C. § 360f(a); 21 CFR § 895.21(a)(3).

[40] http, //www.disabilityrightsintl.org/wordpress/wp-content/uploads/USReportandUrgentAppeal.pdf.

[41] http, //www.ohchr.org/Documents/HRBodies/HRCouncil/RegularSession/Session22/A-HRC-22-53-Add4_EFS.pdf.

[42] http, //boston.com/news/daily/15/school_report.pdf.

model are not adequately assessed, monitored or addressed." Professional and advocacy organizations in the field of developmental disabilities have issued position statements that are categorically opposed to the use of all aversive procedures, including electric shock, in the treatment of persons with intellectual and/or developmental disabilities, because of the risks they pose to patients. Finally, members of the public and national and state/local organizations have advocated for elimination of the use of electric shock interventions because of the risks they pose to patients,[43] both by picketing and by letters to the Agency.[44]

In response to these concerns, the Agency is reviewing the available evidence regarding the risks and potential benefits of, and alternatives to, aversive conditioning ESDs for self-injurious and aggressive behavior under the regulatory framework governing FDA-regulated devices, and is considering banning these devices, as discussed above. Additional clinical data, such as data obtained from well-controlled clinical investigations, would better inform the assessment of the risks and benefits of these devices, and would be required if an application for premarket approval were required for these devices. However, in considering the possibility of clinical studies on these devices, FDA has identified serious concerns regarding the protection of the rights, safety, and welfare of any subjects in such a study, and the permissibility of such studies under FDA's human subject protection regulations, particularly with respect to any study involving children, which appears to be the primary population on whom these devices are used. This section discusses these concerns, primarily under the human subject protection framework for studies involving children under 21 CFR part 50, subpart D. It is important to note that central to this framework is an assessment regarding whether a device's anticipated benefits justify its risks in light of available alternatives.

6.1 Concerns Regarding Risk and Potential Benefit in Clinical Studies of ESDs

The decision to use a medical treatment for an individual patient in the clinical setting involves a judgment that the potential benefits of treatment justify the risks, and that these risks and benefits are at least as favorable as those offered by any available alternatives. In the clinical investigation setting, this judgment is codified in FDA regulations (21 CFR 50.52) that provide additional safeguards to children who are enrolled in FDA-regulated clinical trials. For devices such as ESDs that present more than minimal risk, the criteria for allowing a device to be used in a clinical investigation include the requirements under 21 CFR 50.52 that (1) the risks of the intervention or procedure are justified by the anticipated benefit to the subjects; and (2) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

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[43] See e.g. Boards of Directors, American Association on Intellectual and Developmental Disabilities and The Arc of the United States (2010), available at http, //www.thearc.org/page.aspx?pid=2365; or TASH http, //tash.org/advocacy-issues/restraint-and-seclusion-aprais/overview-of-ars/.

[44] See e.g. http, //www.autistichoya.com/2013/01/judge-rotenberg-center-survivors-letter.html; http, //www.boston.com/bostonglobe/editorial_opinion/blogs/the_angle/2012/06/time_for_mass_1.html; Letter to Margaret Hamburg, dated February 12, 2013 http, //autisticadvocacy.org/2013/02/letter-to-food-and-drug-administration-on-the-judge-rotenberg-center/.

In general, the least restrictive treatment intervention that is effective should be used, in this case to curtail self-injurious and aggressive behavior (see, e.g., Fox 2005). There appears to be little disagreement that ESDs for aversive conditioning in patients exhibiting SIB and aggressive behavior are a highly restrictive intervention. Therefore, in order for the balance of risk and potential benefits of aversive conditioning ESDs for self-injurious and aggressive behavior to be at least as favorable to subjects as available alternatives, as required by 21 CFR 50.52, the use of aversive conditioning ESDs would need to be limited to persons who are refractory to or unable to tolerate adequate treatment attempts of all other less restrictive modalities of treatment administered by appropriately qualified clinicians. This is reflected in the cleared indications for use for JRC's GED device, which provide, "The device should be used only on patients where alternate forms of therapy have been attempted and failed." As summarized in section 7 below, the Agency is aware of no rigorous or systematically collected data that would inform the question of whether a population exists that is appropriately refractory. However, there is some evidence that alternative treatments (e.g. positive behavioral supports along with pharmacological therapy) appear to be effective in some severely affected children, and may have more tolerable side effects (Cole and Levinson, 2002; Horner et al., 2005; LaVigna et al, 2012; McClean et al., 2007; Pace et al., 2005; Rothwell et al., 1999, and Toussaint and Tiger, 2012).

Even if a patient population can be identified that is refractory to available alternative treatments, the risks of using ESDs for aversive conditioning must still be justified by the prospect of direct benefit for that population to be approvable under 21 CFR 50.52. Therefore, the next question is whether (in this refractory population) the benefits of a reduction in self-injurious or aggressive behaviors can be considered to justify the risks associated with the use of the device. In addition to evaluating the probability of harm from use of an aversive conditioning ESD, answering this question requires an evaluative comparison of the harms that may be prevented with treatment versus the harms that are caused by the treatment (Rossi and Nelson, 2012).

The FDA literature review identified case reports and case series suggesting the short term effectiveness of ESDs for reducing self-injurious or aggressive behaviors, but raised concerns due to the lack of long-term effectiveness data and the numerous potential serious risks identified. Even if the device is effective in the short term at altering problem behaviors, there are still questions regarding whether its risks are justified given these potential harms. The absence of systematic data establishing the effectiveness of the devices makes the study of ESDs for aversive conditioning more difficult to justify. For all of these reasons, the Agency is concerned that the harms associated with the use of ESDs for aversive conditioning may not be justified by the potential benefits, even in populations that may be considered "refractory". Therefore, the Agency is concerned that the investigational use of these devices may not be approvable under 21 CFR 50.52.

6.2 Investigational Use of ESDs for Aversive Conditioning under Other Portions of 21 CFR 50 Subpart D

Should a clinical investigation using ESDs for aversive conditioning not be approvable under 21 CFR 50.52, there are three additional categories of clinical investigations in children that may be considered under FDA regulations at 21 CFR 50 subpart D. These categories include

investigations that pose no more than minimal risk (21 CFR 50.51), or a minor increase over minimal risk (21 CFR 50.53), and a category for investigations that are not approvable under §50.51, §50.52, or §50.53 (21 CFR 50.54).

Due to the seriousness of the known risks of ESDs, the Agency has determined that the risks of ESDs for aversive conditioning exceed minimal risk (21 CFR 50.51) or a minor increase over minimal risk (21 CFR 50.53). Therefore, an investigation in which ESDs for aversive conditioning would be used is not approvable under either of these categories. The remaining category under which a research protocol using ESDs for aversive conditioning in children might be considered (21 CFR 50.54) involves referral by an IRB, consultation with the Pediatric Advisory Committee, and a final determination by the FDA Commissioner that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; that the clinical investigation will be conducted in accordance with sound ethical principles; and that adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in §50.55. The Agency is concerned that a study using ESDs for aversive conditioning does not meet these criteria.

Finally, an adequate assent/permission process as required under 21 CFR 50.55 does not make an otherwise impermissible study permissible. Thus, until the Agency determines that a study could be designed that is both scientifically sound and ethically justified; it would not be justifiable to ask subjects to enroll.

Although the above analysis applies to the investigational use of ESDs for aversive conditioning in children, there is also concern about the acceptability of the use of these devices in adults. This is especially true for adults who are not capable of providing informed consent, since the same vulnerability exists that supports the need for additional safeguards for pediatric studies, as provided by 21 CFR part 50 subpart D. In investigations on both pediatric and adult subjects, FDA regulations at 21 CFR 56.111 require that the risks of the study are minimized, the risks are reasonable in relation to anticipated benefits and knowledge that may be expected to result from the study, and that selection of subjects for the study must be equitable. FDA would have concerns that the risks to subjects are not appropriately minimized, and the rights, safety, and welfare of subjects, particularly ones with developmental disabilities, would not be adequately protected if a less restrictive therapy exists with a more favorable risk/benefit profile.

Finally, there are practical limitations on any data that might be collected in a clinical trial of aversive conditioning ESDs. As discussed above, as far as FDA is aware, ESDs for aversive conditioning are only in use at a single institution in the U.S. (JRC). Conducting a study at a single institution would limit the generalizability of the study results. Study results would be difficult to interpret due to the unavoidable confounding effect of other treatments the subjects receive. Attempts to assess the psychological benefits or harms of device use would likely be similarly confounded. Although the risks of a retrospective study that examined existing patient records for evidence of safety and effectiveness of ESDs may be permissible under FDA regulations, the ability of such data to provide sufficient valid scientific evidence to support a reasonable assurance of safety and effectiveness is questionable. Thus, it is unclear

whether scientifically credible and ethically appropriate studies could be designed to establish the safety or effectiveness of these devices.

6.3 Clinical Use of ESDs for Aversive Conditioning

When the U.S. National Commission published in 1978 the seminal report on research involving children that became the basis for the current federal regulations, they explicitly modeled the criteria balancing risk and potential benefit under 21 CFR 50.52 on considerations a clinician would use when determining whether a particular intervention or procedure would be appropriate for their patient.[45] This provides grounds for expanding the previous discussion regarding risks and potential benefits of the device in the investigational context into the clinical context. Thus, the Agency is also concerned that the harms associated with the use of ESDs for aversive conditioning in the clinical setting may not be justified by the potential benefits, even in populations that may be considered "refractory."

7 Summary

FDA is considering issuing a ban on ESDs for aversive conditioning that are intended to administer a noxious electrical stimulus to patients exhibiting self- injurious behavior (SIB) and aggressive behavior because, in light of other available treatment options and new information, FDA is concerned that they present a substantial and unreasonable risk of illness or injury. FDA is convening this Advisory Panel meeting to seek scientific and clinical expert opinion on the risks and benefits of these devices and to obtain recommendations that will assist the Agency in deciding whether or not to ban these devices. Section 516 of the Food Drug & Cosmetic Act (the Act) authorizes FDA to ban, by regulation, any device intended for human use that "presents substantial deception or an unreasonable and substantial risk of illness or injury."[46] When making this decision FDA must weigh the benefits with the risks of these devices. All available data and information must be considered, including the benefits and risks associated with other available treatments.

7.1   Other Available Treatments for SIB and Aggressive Behavior

Since the decision to ban a device must be made in consideration of the available alternative treatments, FDA provided information on a number of treatment options for patients exhibiting SIB including aggressive behaviors. These options include pharmacological, behavioral, and other non-electrical therapies. Currently, there are no published consensus guidelines or practice parameters for the treatment of SIB and aggressive behavior for individuals with limited intellectual ability or development disabilities. A review of the published literature suggests that behavioral treatments should be the first line treatment, notably when environmental factors contributing to occurrence of SIB and aggressive behavior can be identified. However, there does not appear to be any consensus in the literature regarding the type of behavioral intervention that should be employed first. Pharmacological interventions

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[45]   Department of Health, Education, and Welfare (DHEW), Office of the Secretary. Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Federal Register. 1978; 2084-2114, page 2086.

[46]   21 U.S.C. § 360f (a).

are typically used in conjunction with a behavioral treatment program or when patients do not respond to a behavioral therapy.

The majority of the treatment studies are limited to either a single case report or a small case series. Despite the numerous methodological limitations of the published literature, overall both pharmacological and behavioral interventions appear to be relatively successful in reducing but not completely eliminating SIB and aggressive behavior in persons with intellectual and developmental limitations. Reporting of adverse events, with the exception of pharmacological studies, is sparse, and few behavioral studies report adverse events. There are only two pharmacological treatments for autism spectrum disorders approved by FDA, risperidone and aripiprazole. The adverse event profiles of antipsychotic agents, such as risperidone and aripiprazole appear to be similar to that reported for major psychiatric disorders and includes sedation, weight gain, development of involuntary movements (e.g., tardive dyskinesia, dystonia. akathesia), elevated prolactin levels, cardiac conduction changes and neuroleptic malignant syndrome (McDougle et al, 2002; Matson et al, 2008; Robb, 2010). Some of the more common adverse events associated with other pharmacological treatments (SSRIs, tricyclic antidepressants, opioid antagonists, mood stabilizers, and alpha agonists), are, headache, hyperactive behavior, gastrointestinal effects, anxiety, sexual dysfunction , weight gain, dry mouth, sedation, changes in appetite, and skin rashes. Mood stabilizers, including lithium and anticonvulsant agents, often require monitoring of cardiac function, kidney function, and routine blood tests to assess for evidence of toxicity that can be associated with several serious adverse events, including coma and death.

> The Panel will be asked to discuss whether they believe there are effective treatment alternatives, both FDA approved or used in the practice of medicine, to ESDs for aversive conditioning that are intended to administer a noxious electrical stimulus to a patient exhibiting SIB and aggressive behavior and if so, they will be asked to discuss the benefits of these treatments as compared to the risks.

7.2   Benefits and Risks of ESDs for Aversive Conditioning

FDA provided a discussion of the benefits and risks associated with ESDs for aversive conditioning for several indications, including SIB and aggressive behaviors associated with developmental disabilities. The information consists of published scientific literature, information provided to FDA, independent reports, information from other federal agencies, public hearings, clinical interviews conducted by FDA, and media reports. The published scientific literature represents the highest quality information available, but given the absence of systematically conducted, well-controlled, prospective investigations, any conclusions should be cautiously considered.   In contrast to the systematic literature review, information from the other sources may be more susceptible to bias given the lack of peer review, the motivations of the authors, and the circumstances in which the information was presented. Therefore, this information should also be cautiously considered.

7.2.1 Benefits

The literature review and other sources of information suggest that short-term benefit is supported, while significant concerns exist about the long-term effectiveness. The FDA

literature review results are similar to that of two noted researchers in the field (Skinner and Lovaas), who also concluded that punishment methods (Skinner) and ESD for aversive conditioning (Lovaas) demonstrate short-term benefit but lack demonstrated long-term durability. However, there are concerns regarding the quality of available information as noted in the preceding section.

> The Panel will be asked to discuss whether the available evidence demonstrates ESDs for aversive conditioning intended to deliver a noxious stimulus to a patient exhibiting SIB and aggressive behavior is an effective treatment and if so, for what specific population(s) of patients has effectiveness been demonstrated.

7.2.2 Risks

Patients may experience adverse physical and psychological harms from the use of ESDs for aversive conditioning.   The following potential risks were identified by the FDA from literature review and other sources of information, other negative emotional reactions or behaviors, burns and other tissue damage, anxiety, acute stress/PTSD, fear and aversion/avoidance, pain/discomfort, depression (and possible suicidality), substitution of other negative behaviors (including aggression), device malfunction, psychosis, and neurological symptoms and injury.

It should be noted that the published literature suffers from evolving standards of AE reporting (i.e., more recent publications are more likely to present adverse events) with 26 of 45 articles being published before 1980. Of the 45 articles reporting clinical data, 17 contained no report of whether subjects experienced AEs (or not), and only 3 reported any systematic method to monitor AE's.

> The Panel will be asked whether the FDA has provided a complete list of risks and whether there any additional risks that you think should be included.

7.2.3 Treatment Resistance

When treating persons with developmental or intellectual disabilities, the behavioral intervention should be the least restrictive option available that still results in behavior reduction (Foxx, 2005). The balance of risk and potential benefit of using aversive conditioning ESDs would be most favorable in a population that is refractory to less invasive treatment modalities. FDA is not aware of any criteria identifying refractory patients or any rigorous or systematically collected data that would inform the question of whether a population exists that is refractory to adequate trials of other available treatment modalities, provided by appropriately qualified clinicians, or who are unable to tolerate such treatment modalities due to side effects. Anecdotal reports may be found of persons who were apparently refractory to all behavioral controls except ESDs for aversive conditioning(Israel et al., 2008) along with reports of persons who were successfully treated with less restrictive methods after ESDs for aversive conditioning were previously used (Bird and Luiselli, 2000).

The Panel will be asked to consider whether there is a specific population of patients that is refractory to adequate treatment attempts using other available treatment options, and for whom these devices would be the only effective treatment in which the benefits outweigh the risks.

7.3   Labeling and Restrictions on Device Use

Before banning a device, FDA must make a specific determination that the substantial deception or unreasonable and substantial risk cannot be eliminated by a change in the labeling for the device.   Additionally there may be other mitigations, such as device restrictions, that could correct or eliminate any unreasonable and substantial risks posed by the device. Examples of potential risk mitigation through labeling or other restrictions include but are not limited to,

- Device technological restrictions (e.g., electrical stimulation output parameters, limitation of number and locations of electrode permitted on an individual, etc.).

- Labeling restrictions (e.g., use in treating only certain populations (e.g., treatment refractory patient populations, patients in certain age groups, etc.) or use in treating only when significant (e.g., life-threatening) self-injurious and/or assaultive/aggressive behaviors are being exhibited.).

The Panel will be asked to comment on whether labeling or any other mitigation, such as restricting use of the device, could correct or eliminate a substantial and unreasonable risk of illness or injury for any population and if so, they will be asked to identify the labeling change or restriction, and discuss how it will address the risk.

7.4   Assessment of Unreasonable and Substantial Risk

Section 516 of the FD&C Act (21 U.S.C. § 360f) sets forth the standard for banning devices. Under that provision, in order to ban a device, FDA must make a finding that a device "*presents an unreasonable and substantial risk of illness or injury*" based on all available data and information (21 CFR 895).

The Panel will be asked to discuss whether the device presents a substantial and unreasonable risk of illness or injury.   In their response they will be asked to consider the benefits in relation to the risks, in light of other available treatments, whether there is a specific population of patients for which these devices would be the only effective treatment, and explain their reasoning.

7.5 Additional Question

Additionally, as part of its banning analysis, FDA must consider whether devices should be removed from those currently receiving treatment.

If the Panel recommends f FDA determines that the devices present an unreasonable and significant risk of illness or injury, they will be asked to discuss whether devices should be removed from patients currently receiving treatment.

7.6 Ethical Considerations Related to Clinical Studies

If it is determined that clinical data on ESDs for aversive conditioning is needed, the question of whether a clinical trial can be conducted is raised. However, there are ethical concerns with the use of ESDs for aversive conditioning intended to deliver a noxious stimulus to a patient exhibiting self-injurious behavior (SIB) and aggressive behavior and FDA is concerned that, due to the known risks of ESDs and possible alternatives, the use of these devices in clinical studies, particularly studies in children, may not approvable under FDA regulations.

The Panel will be asked to discuss the circumstances, if any, under which a clinical trial could be conducted to evaluate ESDs for aversive conditioning for the treatment of SIB and aggressive behavior, such that the risks to the subjects are outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained.

Appendix I: Summary of JRC Patient Data

As indicated in Section 5.3.6.4, during the first quarter of 2013, JRC provided the FDA Office of Compliance with comprehensive treatment summaries for each student receiving aversive conditioning with ESDs. The records indicate that as of February 8, 2013, 86 students had court-approved treatment with the GED device. Of these, 66 students had treatment plans that included the use of the GED device. The records were reviewed by the FDA and are summarized in Table 6 below with all patient identifiers removed. Many patients were treated with GED-4, which has an output stimulation current about three times that of the FDA cleared GED device (Israel et al., 2008). The age range of patients being treated at the time the records were reviewed was between 14 and 50 years (Mean: 30.2 ± 11.5 years) and there were 72 males and 18 females. Treatment duration was difficult to determine as only the admission date to JRC was provided in these case histories. Diagnoses included various levels of mental retardation, severe behavior disorder, autism, pervasive developmental disorder, seizure disorder, attention deficit hyperactivity disorder, and a variety of medical disorders (e.g., Angelman's syndrome). The target behaviors for the GED primarily involved SIB and aggressive behavior but also included physical and sexual assaultive behavior, pica, and destructive behavior. According to the records no adverse events were reported for any of the patients.

Table 5, Data from JRC Patient Records provided to the FDA/CDRH Office of Compliance

Diagnosis[1]	Device Used	Target Behavior	Reported Adverse Events
MR, Autism, Seizures	GED-4[2]	Aggression	None
MR, Autism, Severe Behavioral Disorder	GED-4[2]	SIB	Not stated
Mild MR, Severe Behavioral Disorder	GED-4[2]	SIB, aggression	None
Autism, Profound MR	GED	SIB, aggression	None
Autism, MR, Severe Behavior Disorder	GED-4[2]	SIB, aggression	None
MR, Autism	GED	SIB, aggression	None
MR, PDD	GED-4[2]	SIB, aggression	None
Autism, Severe Behavior Disorder	GED	Aggression	None
Schizophrenia, Depression, MR	GED	Assault	None
MR, Autism, Severe Behavior Disorder	GED-4[2]	SIB, aggression	None
Autism, MR, Severe Behavior Disorder	GED	Aggression, SIB	None
ADHD, ODD, Severe Behavior Disorder	GED	Aggression	None
MR, Autism, Seizure	GED	Aggression, SIB	None
Down's, Severe Behavior Disorder	GED-4[2]	SIB,	None

Diagnosis[1]	Device Used	Target Behavior	Reported Adverse Events
Autism, MR, Severe Behavior Disorder	GED	Aggression	Not stated
Autism, MR, Severe Behavior Disorder	GED-4[2]	Aggression, SIB	None
Autism, MR	GED	Aggression, SIB	None
MR, Autism	GED	Aggression SIB	None
Autism, MR	GED	Aggression, SIB	None
Autism, MR, Severe Behavior Disorder	GED-4[2]	SIB, aggression	None
Autism, MR, Severe Behavior Disorder	GED	SIB, aggression	None
Autism, MR, Severe Behavior Disorder	GED	SIB, physical outbursts	None
Mild MR, ADHD, Antisocial Personality, Severe Behavior Disorder	GED	Aggression, dangerous behavior	None
Autism, Mild MR, Seizure, Severe Behavior Disorder	GED	Dangerous behavior, aggression, SIB	None
Autism, MR, Severe Behavior Disorder	GED	SIB, aggression	None
OCD, PDD, Autism, MR, Severe Behavior Disorder	GED	Dangerous aggression, SIB	None
Mild MR, Intermittent Explosive Dis., Fetal EtOH, Severe Behavior Disorder	GED	Severe aggression, suicidal behavior	None
PDD, Mod. MR, Severe Behavior Disorder	GED	Dangerous aggression, SIB	None
Severe Intell Disability, Autism, Severe Behavior Disorder	GED	Dangerous behaviors, SIB	None
MR, Autism, Seizures, Severe Behavior Disorder	GED	Dangerous behaviors, SIB	None
Severe MR, Autism, Severe Behavior Disorder	GED	SIB, aggression	None
Autism, MR, multiple congenital anomalies, congenital heart disease, Severe Behavior Disorder	GED	SIB, aggression	None
Autism, Mild MR, Severe Behavior Disorder	GED	SIB, dangerous aggression	None
Autism, Severe MR, Severe Behavior Disorder	GED	SIB, aggression	None
Mod MR, PDD, seizure, Severe Behavior Disorder	GED	Severe aggression	None

Diagnosis[1]	Device Used	Target Behavior	Reported Adverse Events
Autism, Severe MR, Severe Behavior Disorder	GED-4[2]	SIB	None
PDD, Autism, MR, Severe Behavior Disorder	GED	Dangerous aggression, SIB	Not stated
Autism, MR, Severe Behavior Disorder	GED	SIB, aggression	None
Profound MR, PDD, seizures, Severe Behavior Disorder	GED-4[2]	Dangerous aggression, SIB	None
Autism, MR	GED-4[2]	SIB, aggression	None
PDD, MR,	GED	SIB, aggression	None
Schizoaffective, Borderline Personality, Severe Behavior Disorder	GED	SIB	None
Autism, MR, Severe Behavior Disorder	GED-4[2]	SIB, dangerous aggression	None
Autism, Mod MR	GED-4[2]	Aggression	None
Autism, MR, Landau-Kleffner, Seizure, Severe Behavior Disorder	GED	SIB, dangerous aggression	None
Autism, MR, Severe Behavior Disorder	GED	SIB, dangerous aggression	None
MR, Severe Behavior Disorder	GED	SIB, dangerous aggression	None
MR, Severe Behavior Disorder	GED	SIB, dangerous aggression	None
Asperger's, OCD, Severe Behavior Disorder	GED	SIB, dangerous aggression	None
Autism, MR, Severe Behavior Disorder	GED-4[2]	SIB, dangerous aggression	None
Severe MR, Autism, seizures	GED	Aggression, SIB	None
PDD, Moderate MR	GED	Dangerous aggression, SIB	None
Autism, Severe MR, Severe Behavior Disorder	GED-4[2]	Dangerous aggression, SIB	None
Mild MR	GED	Dangerous aggression, suicidal gestures, sexual aggression	None
Intell. Disability, MR, Autism	GED	Dangerous aggression SIB	None
Autism, Severe MR	GED-4[2]	Dangerous aggression, SIB	None
Autism, MR	GED-4[2]	Dangerous aggression, SIB	None

Diagnosis[1]	Device Used	Target Behavior	Reported Adverse Events
Severe MR, Autism, Severe Behavior Disorder	GED-4[2]	Dangerous aggression, SIB	None
Autism, MR	GED-4[2]	Dangerous aggression, SIB	None
PDD, Severe MR, Severe Behavior Disorder,	GED	Dangerous aggression, SIB	None
Profound MR, Seizure, Angelman's, Severe Behavior Disorder	GED	Dangerous aggression, SIB	None
Severe MR, Autism	GED-4[2]	Dangerous aggression, SIB	None
Autism, Severe MR	GED	Dangerous aggression, SIB	None
Mod MR, Autism, Severe Behavior Disorder	GED-4[2]	Dangerous aggression, SIB	None
Autism, Severe MR, Severe Behavior Disorder	GED-4[2]	Dangerous aggression, SIB	None
Autism, Profound MR, Severe Behavior Disorder	GED	Dangerous aggression	None
PDD, Mod MR, Severe Behavior Disorder	GED	Dangerous aggression, SIB	None
MR, Mood Disorder, Intermittent Explosive Disorder, ADHD	GED	Dangerous aggression, assault, sexual assault, property destruction	None
Severe MR, Autism	GED	SIB, dangerous aggression	Not stated
Moderate MR, PDD	GED	Dangerous aggression,	None
Autism, MR, Severe Behavior Disorder	GED	SIB, pica, dangerous aggression	None
Autism, Mod MR	GED	Aggression, SIB	Not stated
Autism, MR, seizure, Severe Behavior Disorder	GED	SIB, dangerous aggression	None
Mild MR, Intermittent Explosive, Antisocial Personal, Severe Behavior Disorder	GED-4[2]	SIB, pica, violent assault	None
Autism, MR, Severe Behavior Disorder	GED-4[2]	SIB, aggression	None
Autism, MR, Severe Behavior Disorder	GED	Dangerous aggression, SIB, pica	None
Autism, MR, Severe Behavior Disorder	GED	SIB, dangerous aggression	None
Mild MR, Severe Behavior Disorder	GED	Dangerous aggression, SIB	None

Diagnosis[1]	Device Used	Target Behavior	Reported Adverse Events
Autism, MR	GED	Dangerous aggression, SIB	None
Seizures, Severe MR, Tuberous Sclerosis, Severe Behavior Disorder	GED	Violent aggression, SIB	None
Moderate MR, PDD	GED	Assaultive behaviors, property destruction	None
Mild MR, Bipolar, Seizures, Severe Behavior Disorder	GED-4[2]	Dangerous aggression, SIB, pica	None
Severe MR, Autism, Arnold Chiari Malformation	GED	Dangerous aggression SIB	None
Borderline Intelligence, Asperger's, Severe Behavior Disorder	GED	Dangerous aggression	None
Severe MR, Autism, Severe Behavior Disorder	GED	Dangerous aggression destructive	None
Autism, Mod MR	GED	Dangerous aggression SIB	None
Autism, MR	GED	Dangerous aggression, SIB	None
MR, PDD, Landau-Kleffer, Seizures, Severe Behavior Disorder	GED	Dangerous aggression SIB	None
Profound MR, Autism, Severe Behavior Disorder	GED	Dangerous aggression, SIB	None

[1]   MR=mental retardations, ADHD=attention deficit hyperactivity disorder, PDD=pervasive developmental disorder, OCD=obsessive-compulsive disorder

[2]   The GED-4 is not cleared for marketing by the FDA. The output stimulation current of the GED-4 is reported to be three times that of the FDA cleared GED device (Israel, 2008).

Appendix II: References

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