LESSONS FROM HISTORY

Flashback to the 1960s: LSD in the treatment of autism

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Abstract
Between 1959 and 1974, several groups of researchers issued reports on the use of d-Lysergic Acid Diethylamide (LSD) in the treatment of children with autism. This paper reviews that literature to consider how the authors justified these studies, as well as their methods, results, and conclusions. The justification for using LSD was often based on the default logic that other treatment efforts had failed. Several positive outcomes were reported with the use of LSD, but most of these studies lacked proper experimental controls and presented largely narrative/descriptive data. Today there is renewed interest in the use of psychedelic drugs for therapeutic purposes. While this resurgence of research has not yet included children with autism, this review of the LSD studies from the 1960s and 1970s offers important lessons for future efforts to evaluate new or controversial treatments for children with autism.

Keywords: Autism, LSD

Introduction
Ever since Kanner first described autism in 1943, researchers have struggled to explain and effectively treat this perplexing disorder [1]. Various etiological theories have been proposed, ranging from Kanner’s original albeit often forgotten conclusion that the condition was probably biological in origin, to more psychoanalytic accounts [2]. A prevailing view in the 1950s and 1960s was that autism represented a childhood version of adult psychosis or schizophrenia [3]. Consistent with this conceptualization, treatment was firmly rooted in the clinical psychiatry of the day. By the early 1960s, numerous biologic treatments (e.g., electric convulsive shock, sub-shock insulin, amphetamines, and antidepressants) had been used in an attempt to help children with autism [4]. This is a brief historical review of one such treatment; the psychedelic drug known as LSD.

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treatment of children with autism. This paper provides a historical review and methodological critique of the use of LSD in the treatment of children with autism and related disorders. We consider the justification offered for these studies, as well as their methods, results, and conclusions.

From today’s perspective, LSD might appear to be one of the more peculiar approaches to the treatment of autism with little contemporary relevance. However, there is renewed interest in the use of LSD for therapeutic purposes [5]. Once again researchers are focusing on evaluating the potential of LSD and other psychedelic drugs for treating a range of problems, such as post-traumatic stress [6] and anxiety [7]. Given this renewed interest it would seem timely to re-evaluate the literature from the initial era of LSD experimentation on children with autism. Doing so may highlight important lessons that should be considered when designing research to evaluate new or controversial treatments. In addition, because few of our contemporaries seem aware that research of this nature had once been conducted, we thought a review of this literature might not only be of interest to readers, but also stimulate thoughtful reflection on contemporary autism practice, which is littered with unproven, ineffective, and possibly harmful treatments [8].

Background: Albert Hofmann’s problem child

In 1943 the Swiss chemist Albert Hofmann accidentally discovered the psychedelic properties of LSD [9]. The manner is which this discovery was made is a classic illustration of the role and value of serendipity in scientific discoveries so well documented by Gest [10]. Briefly, in 1938 Hofmann produced the substance known as LSD or more technically LSD-25, so called because it was ‘the twenty-fifth substance in this series of lysergic acid derivatives’ [9, section 1.3]. It was thought that this new drug might have some potential as a circulatory and respiratory stimulant, but initial animal tests were rather uninteresting and so the project was discontinued. Five years later, Hofmann synthesized some more LSD for further testing. In the process he accidentally absorbed enough of the substance to produce the perceptual distortions for which the drug is so infamous. He reported feeling restless, dizzy, and having an extremely stimulated imagination consisting of a stream of ‘fantastic pictures, extraordinary shapes with intense kaleidoscopic play of colors.’ [9, section 1.4]. These feelings and sensations, he noted, were not unpleasant.

Shortly after this accident he deliberately ingested a very small amount of the substance (0.25 milligram) to confirm that LSD-25 was in fact responsible for the strange effects he had experienced a few days earlier. Within 40 minutes he began to experience similar symptoms, but this time the effect was not so pleasant. Instead he found the sensations to be rather more disturbing and intense. A few additional self-experiments by Hofmann and colleagues confirmed that LSD was indeed an incredibly powerful intoxicant even in extremely small dosages.

Impressed by these powerful effects, Hofmann’s employer, Sandoz, approved further trials to establish its toxicity and physiological effects. In 1947, Stoll published the results of what appears to be the first human trial, which involved 16 healthy volunteers and 6 patients with schizophrenia [11]. He reported that the drug produced ‘very impressive disturbances of perception and visual hallucinations’ (p. 279), but also appeared to induce vegetative-like states and some motor control problems. Stoll took some LSD himself, extending Hoffman’s precedence of self-experimentation. (Parenthetically, while no substitute for the randomized controlled trial, self-experimentation has a legitimate role in treatment evaluation and may enable researchers to gain some understanding of the effects of any treatment that they seek to use with children. Gandevia [12] outlined several methodological and ethical issues that need to be considered in self-experimentation.) Under the influence of LSD, Stoll initially enjoyed the condition and felt rather euphoric. But his euphoria soon turned to depression, which lingered for several days.

Depression aside, Hofmann and others at Sandoz agreed that Stoll’s trial had demonstrated some clinical potential for LSD. It was soon marketed as an experimental drug for the study of psychosis and as a possible facilitator of psychotherapy. They made the drug freely available to researchers and medical personnel for such experimental and clinical purposes. Several autism researchers were among those who made use of the newly available substance.

The Autism/LSD studies

The first public reports on the use of LSD in the treatment of children occurred in 1959 at a conference in Princeton New Jersey [13]. The conference was devoted to the use of LSD in psychotherapy and included several independent references to its use with autistic-schizophrenic children. A summary published the following year included comment on five such studies [13]. As noted by Rhead [14], while these initial reports
lacked critical detail, the results were considered ‘quite promising in a number of cases.’ (p. 93).

A more formal study by Freedman, Ebin, and Wilson appeared in print two years later [15]. It is worth considering the Freedman et al. study in some detail because their methodological approach is fairly typical to that of many subsequent LSD studies. Freedman et al. gave LSD to 12 ‘autistic schizophrenic’ children. The sample consisted of 10 boys and 2 girls who ranged from 5 years 11 months to 11 years 10 months of age. Varying dosages of LSD (either 50, 100 or 200 μg) were given on one or two occasions. The drug was administered orally as the child arrived at school in the morning. The children were continually observed for the next several hours with ‘Careful notes . . . taken of all physiological and mental changes . . .’ (p. 39).

The researchers noted that the signs of LSD inebriation became apparent within 15–30 min with the effect lasting 4–5 hours. Physiologically not too much happened. Some children became flush and their pupils dilated, but neither pulse nor blood pressure showed much change. Behaviourally, the effects varied. Three children were said to show evidence of catatonia (e.g., strange, fixed position of hands, bizarre postures, waxy flexibility of arms). None of the children ate their lunch until the drug wore off. Freedman et al.’s narrative description of the children’s behaviour under LSD includes reference to increased physical contact, disappearance of physical mannerisms, and development of what were interpreted as new bodily sensations. These apparently new bodily sensations were evidenced by the fact that ‘. . . all but four of the children were observed to repeatedly stroke or move a particular area – most often the lips or mouth’ (p. 41). Psychic effects were also noted, including rapid moods swings ‘from extreme elation to extreme depression’, increased anxiety, and signs of both auditory and visual hallucinations (p. 41). The authors were primarily interested in evaluating whether LSD might promote speech, but the ‘hoped for change from muteness to speech did not occur’ (p. 44).

Considering their results in light of previous research on adults with schizophrenia, the authors found ‘little hope for its [i.e., LSD’s] success in the treatment of children’ (p. 44).

Despite Freedman et al.’s pessimistic conclusion, the pace of LSD research accelerated over the next few years. Their less than promising results were countered by assertions that children respond differently to psychedelic agents than adults. Children were not only said to show fewer medication side effects, but they also developed tolerance more slowly and thus could receive larger doses [4]. The emerging journal literature soon included a good number of studies [4,15–21]. By 1969, the volume of literature was sufficient to warrant a systematic review [22].

However, this initial era of legitimate LSD experimentation was already coming to a close by the time this first review was published in 1969. Faced with increasing hysteria and negative publicity stemming from recreational misuse, Sandoz stopped the production and distribution of LSD in 1965 [9]. In the USA, researchers could still obtain supplies from the National Institutes of Mental Health, but the numerous bureaucratic hurdles discouraged research [5]. The last studies to examine the effects of LSD in the treatment of children with autism appeared in the early 1970s [19,21] and the second, more comprehensive review of the literature appeared in 1977 [14].

Thirty years have now lapsed since Rhead’s comprehensive review of research on LSD as a treatment for children with autism and related disorders [14]. From this historical vantage point, and given the renewed interest in psychedelic drugs for therapeutic purposes [5], it would seem timely to re-examine the initial wave of Autism/LSD studies. Consideration of the justification for — and the methods, results, and conclusions of — these studies may offer important lessons for future generations of researchers and clinicians.

**Justification for the LSD studies**

The primary justification offered for the Autism/LSD studies was based on the logic of default. Simply put, nothing much seemed to work very well, so why not try LSD. Simmons et al. [20], for example, employed this logic for their first LSD study. After listing the range of treatments that had been tried up to that point, they correctly noted that: ‘In many instances successful treatment has been largely absent or limited to isolated behavioural changes’ (p. 1201). All seven studies included in the first systematic review of the literature [22] were justified on the grounds that ‘all known forms of treatment had been attempted without success’ (p. 46).

Bender, Goldschmidt, and Siva Sanker [4] were more selective in their application of this logic. They recruited 14 children for an LSD trial on the basis of the fact that these particular children had received ‘a variety of treatments with inadequate response’ (p. 172). Presumably other children were excluded from the study because of their adequate response to some other form of treatment. This selectivity implies that LSD was not the treatment of choice and suggests a hesitancy to employ such a potent medication. Bender and her colleagues were in fact...
...extremely cautious when first using the drug, even obtaining parents’ consent” [23, p. 85].

It should be noted that this brief statement was the only mention of ethical issues among these LSD studies. In the main, ethical issues and parental consent were simply never mentioned. It is therefore unclear if the parents had ever been consulted or informed about the use of LSD in the treatment of their children. In fairness to the investigators, it should be noted that this situation was not unique to research involving LSD, but rather reflects the fact that in the 1960s and 1970s, procedures for obtaining ethical clearance and parental consent were not as formalized as today. Even if ethical clearance and parental consent had been obtained, it is not necessarily the case that researchers would have included these details in the formal write-up of their results.

Ethical issues aside, the logic of default leaves much to be desired as a process for making treatment decisions. Evidence-based practice dictates that treatment recommendations should be based on the best available evidence and less on the trial and error approach associated with the logic of default [24]. Still, the logic of default was compelling at the time. Back then, 30–40 years ago, most children with autism did not respond very well to the range of treatments that had been attempted. Effective, evidence-based treatments simply did not exist. None of the biologic (e.g., electric convulsive shock, sub-shock insulin, amphetamines, antidepressants) or psychoanalytic treatments had met with much success and behavioural intervention was in its infancy.

Today the situation is vastly different. Effective, evidence-based procedures exist for addressing many of the core behavioural deficits and excesses that define autism [25]. The most effective procedures are behavioural in orientation and based on the principles of applied behaviour analysis [26]. Indeed, early and intensive application of behavioural treatment can lead to dramatic improvement in intellectual and adaptive behaviour functioning for some children with autism [27,28]. While individuals will vary in response to such treatment, the consistently positive results from well-designed behavioural interventions make it the treatment of choice for children with autism.

Given today’s solid empirical support for behavioural interventions, the logic of default can no longer be used to justify research with controversial treatments. A higher standard must be expected in any such research programmes that might be initiated in the future. It is not enough to compare a novel approach to no treatment or to a placebo. Rather the new approach should be compared to some well-established procedure [29], provided of course that well-established alternatives do in fact exist. In the case of autism, well-established, empirically-supported treatments exist in the form of behaviourally-based interventions. Any future research into the effects of psychedelics — or any controversial treatment for that matter — should therefore at some point include comparisons with a well-designed behavioural programme.

The researchers and the research settings

Several independent teams of researchers were involved in the LSD studies that followed Freedman et al.’s pioneering work [15]. Lauretta Bender and her colleagues completed the most extensive research programme in this area, which was reported in a series of papers published between 1962 and 1969 [4,17,18,23]. In the course of this programme, a total of 89 children (aged 6 to 15 years) received LSD. As Rhead noted, ‘Some children were ultimately treated with daily doses of 150 µg for periods as long as two years’ (p. 94). The setting for this research programme was the Creedmore State Hospital in New York.

Bender’s work appeared to have served as the inspiration for another prominent research team led by James Q. Simmons and his colleagues at ULCA [19–21]. This team also conducted their research in an institutional setting. Apart from these two teams with fairly extensive research programmes, the other studies appear to have been isolated projects [e.g., 15,16]. While it is unclear if these various researchers were in direct communication with one another, citation analysis shows clearly that these independent teams were certainly aware of each other’s work. For example, Bender et al’s first paper in 1962 [4], referenced Freedman et al. [15]. Later, in 1966, Simmons et al. [20] referenced both Freedman et al. [15] and Bender et al. [4]. In fact, Simmons et al. [20] indicated that because of the difficulty of assessing the reliability of Bender’s work there was a need to develop more objective criteria and employ better experimental designs to evaluate LSD. Their subsequent studies certainly represent a methodological improvement over the approaches used in prior studies, as described in the next section.

Methodological limitations, results, and conclusions of the LSD studies

The vast majority of the Autism/LSD studies had serious methodological flaws. In most cases, dependent variables were neither operationally defined nor objectively measured [4,15–18,23]. Experimental control was generally nonexistent in that most of the protocols involved an open trial with the drug
given either once or twice [15] or repeatedly for several days, weeks or even months and years in some instances [4,17,18,23]. After the drug was administered the children were observed and their reactions recorded in narrative format. Observations were naturalistic with little apparent appreciation for the value of controlling the conditions under which observations were made. The observers themselves were not blind to the fact that the children had received the medication, and the reliability of their narrative descriptions was never assessed. The resulting data are for the most part purely qualitative and presented in a narrative form that is highly subjective, potentially biased by observer expectations, and of unknown reliability and validity. These methodological limitations did not escape the notice of reviewers. Mogar and Aldrich [22], for example, noted that the seven studies they reviewed ‘suffer gross shortcomings’ and ‘severe limitations’ (p. 44).

The specific limitations identified by these reviewers included ‘small samples, subjective and vague criteria of drug effects, and improvement, and grossly inadequate follow-up’ (p. 44).

Notable exceptions to these methodological shortcomings are seen in the work of Simmons et al. [19,20]. These studies evaluated the effects of LSD under more rigorously controlled conditions. In addition to operationally defined dependent variables, standardized observations, and objective measurement, the researchers also adopted proper experimental design, specifically a single-subject reversal design [30]. With this design the investigators were able to demonstrate internal validity and replicate the effects of LSD on the children’s behaviour. And yet, while Simmons et al.’s methodology was much stronger than that found in previous studies, these two studies were still rather limited. Their initial experiment with LSD, for example, included only two children [20]. When follow-up work was completed with a larger sample of 17 children, the results were less promising and, as noted later, brought the therapeutic value of LSD into question [19].

The results of LSD treatment for the majority of children with autism who participated in these studies were described in highly positive terms. Bender and her colleagues [4], for example, reported that LSD was well tolerated ‘without side-effects, toxic effects, or other untoward responses’ (p. 173). The children were also said to be making steady progress under LSD. Play behaviours improved and the children were more eager to interact with adults. In addition to increased social responsiveness, skill gains in feeding, toileting, and comprehension of language were also reported and stereotyped movements decreased. On LSD, the children were ‘happier’ and their mood ‘high’. Apparently this latter effect was perceived as a good outcome. Similarly positive descriptions can be found in most of the studies [14]. Overall, reviewers concluded that the effects of LSD treatment were very promising and could even be considered excellent for the majority of children [14,22].

However, such narrative descriptions are difficult to interpret. When researchers report an increase in social responsiveness or improvement in play, it is unclear what if any positive changes occurred and, if so, how much of this change could be attributed to the treatment. Neutral and negative findings were often cast in a more positive light than would seem warranted. Even an increase in aggression, for example, was viewed as positive in Bender et al.’s narrative [23] in that such behaviour was ‘…considered an improvement in that it represented a contact with the environment that was previously ignored’ (p. 62). The tendency to describe potentially problematic changes in a favourable light can also be found in Freedman et al. [15]. As noted before, what might today be viewed as increased stereotyped mannerisms (e.g., stroking of the lips) were interpreted by Freedman et al. as ‘new bodily sensations’ (p. 41).

The general consensus appeared to be that autistic children would be happier, healthier, and more responsive on LSD. In a few short years, these generally positive reports escalated LSD from an experimental drug with some promise to a treatment that could be highly recommended. Mogar and Aldrich [22] concluded that ‘the collective results argue strongly for more extensive use of psychedelic drugs in the treatment of autistic children’ (p. 44). Curiously, this conclusion did not match their own critical appraisal of the quality of the studies, which they found to be seriously flawed.

However, as further evidence accumulated, it soon became clear that the news was not uniformly good. In fact, the promise of LSD proved to be rather short-lived. In addition to Freedman et al.’s initial pessimism [15], Rolo et al. found no evidence that LSD was of benefit to the 12-year-old schizophrenic child that they studied. [16]. And while Simmons et al. initially found consistent and positive changes in the behaviour of their first two subjects (e.g., increased looking at others and laughing) [20], they later noted that many of the 17 children to whom they gave LSD became completely immobile or preoccupied with certain objects [19]. In fact many of these children showed such diminished responsiveness and disturbing responses to LSD that it threw ‘some doubt on its use as a therapeutic adjunct.’ (p. 10). And so, the initial era of LSD experimentation ended where it had begun, with pessimism for the drug’s potential in the treatment of autism.
Conclusion

The major lesson to be learned from this little known set of studies is that all too often controversial treatments are touted as promising on weak evidence and flawed studies. It is extremely difficult to evaluate the evidence from methodologically flawed studies, especially when the available data are largely qualitative (i.e., narrative descriptions). Whatever promise LSD might have had was never going to be validated through these types of studies. Despite the good number of independent studies, it remains impossible to determine whether or not LSD had any therapeutic value for the children with autism who participated in these studies.

This critique of the literature is not meant as an indictment of those researchers who engaged themselves in the study of LSD as a treatment for autism. Scientists were desperate to discover anything that might help these children and at least some researchers considered LSD to be promising [22]. It was reasonable that it should have been subjected to empirical scrutiny. Unfortunately, the methodological tools used by these researchers were incapable of providing convincing data as to LSD’s potential benefit for children with autism.

It is unclear why the weaker narrative/descriptive method was adopted by most of these LSD researchers when the more rigorous randomized controlled trial was not unknown at the time. Perhaps this reflects the difficulty of forming large samples of children with autism given that the condition was not as frequently diagnosed nor as well understood at the time. However, while autism is more frequently diagnosed and better understood today, there has still not yet been a true randomized controlled trial into the treatment of children with autism. In the current best example of a treatment experiment [27], the children were not randomly assigned to the experimental or control groups. Assignment was instead made on an alternating basis depending on the availability of an intervention team.

While carefully controlled randomized controlled trials may be lacking, clinicians can nonetheless draw upon a myriad of well-established intervention procedures [25,26] that have been empirically validated using single-case experimental designs [30]. In the 1960s and 1970s, however, tactics for evaluating treatments using single-case experimental designs were only just developing. The one notable exception, as mentioned before, is the first study by Simmons et al. [20]. These investigators did in fact employ a single-case reversal design to evaluate the effects of LSD on affective responses and social responsiveness, but again that study was limited to only two children with autism.

In any event, judged by the standards expected in today’s randomized controlled trial or the properly controlled and systematically replicated single-case study, the vast majority of these initial Autism/LSD studies were so flawed that the resulting data are little better than anecdote. Does this suggest that researchers should once again consider evaluating LSD’s potential for treating children with autism using more advanced methodological tools? What about related substances, such as MDMA? In considering these questions it is important to stress that the self-experiments described by Hofmann [9] and Stoll [11] provide compelling accounts of the disturbing effects that LSD can produce. Such effects are likely to be incomprehensible to, and thus perhaps even more frightening for most children with autism.

Controversial therapies lacking empirical support are all too commonly used on children with autism [8]. The frequent lack of rational, data-based decision making when it comes to the care, education, and treatment of children with autism is a sad legacy that can be traced back to the earliest misguided attempts to treat children with autism, when all manner of approaches were tried [4]. Professionals must resist the temptation to promote treatments that lack empirical support and should instead be highly critical of unproven treatments. Sound science is necessary to ensure that children with autism receive the best possible treatment. Whether sound science is sufficient to ensure the best possible care for children will depend on how well we can learn the lessons of history.

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References