OUTLOOK

Looking backwards: a possible new path for drug discovery in psychopharmacology

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The history of psychopharmacology is littered with type II errors — the rejection of effective compounds in the specious belief that they were inefficacious because they had failed to beat placebo in a controlled trial. Revisiting some of these drugs to establish their receptor profile, and then determining what patentable compounds now on the shelf match that profile, might represent a possible future pathway to drug discovery. This article looks at the special circumstances in which numerous potentially effective drugs were withdrawn in the United States.

In view of the current slowdown in the development of innovative psychopharmaceuticals, interest has been growing in revisiting successful but now-forgotten compounds of the past[1]. The idea is not to recycle the golden oldies, but to determine the receptor profile of forgotten drugs of proven efficacy, and to determine what patentable compounds today might have a similar receptor profile. Since the introduction of modern psychopharmacology with the first chlorpromazine trials in 1952, thousands of compounds have been synthesized. Many of these have shown efficacy in open-label trials or anecdotally, only to be cast aside in 'type II' error as a result of underpowered controlled trials, often with heterogeneous treatment populations (a type II error means accepting the null hypothesis when it is false). This article considers several of these now-forgotten, but possibly efficacious, compounds, which were withdrawn from the market under rather special circumstances. The Drug Efficacy Study of the National Academy of Sciences (NAS)/National Research Council (NRC) in 1966–1968, and its implementation by the US Food and Drug Administration (FDA) in the years 1968–1974, caused a sweeping reduction of the US pharmacopoeia, known under the bureaucratic acronym DESI (Drug Efficacy Study Implementation).

The Drug Efficacy Study

In accordance with the provisions of the Kefauver–Harris Amendments of 1962 to the Food, Drug and Cosmetic (FDC) Act[2], the FDA committed itself to an assessment of the efficacy of all pharmaceuticals marketed between 1938 and 1962. (From the original FDC Act in 1938 until the passing of the Amendments in 1962, the FDA had considered only safety in drug approvals; most drugs launched before 1938 that were still on the market in the 1960s were retroactively accepted as presumably safe and efficacious.)

Because of the enormity of the task, the FDA gave the NAS/NRC a US $834,000 contract to carry out the review[3]. Between 1966 and 1968, the 30 speciality panels of the NAS/NRC assessed thousands of pharmaceuticals for their presumed efficacy. This was by no means the total number of products on the market, but was merely those for which the FDA requested reviews.

Further sifting then took place as FDA regulators considered the recommendations of the Drug Efficacy Study and began to implement them[4]. DESI resulted in a kind of mass 'weeding out' in the US pharmaceutical market. Of 3,443 drugs considered by the panels, 35% were ultimately withdrawn as a result of regulatory action[5].

The DESI process has never been the object of thorough scholarly study. Previous writers on the efforts of the FDA to clean up the pharmacopoeia have not worked in FDA archives[6], or gone systematically through the day-by-day record of events offered in the pharmaceutical newsletter, *The Pink Sheet* (*F-D-C Reports*). Embarrassed perhaps by the sweeping nature of its own handiwork, the FDA never published a comprehensive list of the drugs it had banned. Instead, individual withdrawals were announced in scattered issues of the Federal Register, a source usually consulted only by lawyers. A comprehensive view of DESI can be gained only by matching decisions announced in the Federal Register to the original decisions of the NAS/NRC panels, documents that are now in the FDA Archives. This article undertakes this matching.

The Psychiatry Panel

At issue here is only the work of the Psychiatry Panel, which was chaired by the Chicago psychiatrist Daniel Freedman and included some of the nation's most distinguished psychopharmacolgists: Jonathan Cole, then at Tufts University and former organizer of the Psychopharmacology Service Center of the National Institute of Mental Health; David Engelhardt, a psychiatrist at the Brooklyn campus of the State University of New York; Leo Hollister of the VA Hospital in Palo Alto, California, a man whom in retrospect might be called the dean of American psychopharmacology; Sidney Merlis at the New York State Hospital in Central Islip; and Karl Rickels of the University of Pennsylvania, an important expert in US drug trials[2]. However, the experience of these highly knowledgeable individuals was with asylum and academic

psychiatry, not with primary care. It should be taken into account that in 1967, at the midpoint of the Psychiatry Panel's work, 70% of psychotropics were prescribed by general practitioners and internists[7].

All of the NAS/NRC panels had been briefed by the FDA to rank drugs according to well-defined categories: effective, probably effective, possibly effective and ineffective. The categories themselves were anything but pillars of scientific exactness, and 'probably effective', for example, was often used as a result of split opinion on a panel. Said William Barclay, a member of one panel: "If all but one member of the panel found the drug effective, you compromise and find it 'probably effective'. You know how committees work"[8].

What the panels did not know, however, was that in implementing the study, the FDA would insist that probably- and possibly-effective drugs be withdrawn within a matter of months if the company did not come up with convincing evidence of efficacy from controlled trials[9]. Rankings such as possibly effective and probably effective turned out to be death sentences if the company was not immediately willing to sponsor large, controlled trials. And in the months after the release of the DESI findings, such trials became the exception rather than the rule, as the companies sought to enlist uninterested academic trialists (doing trials solely for the sake of regulatory approval has never appealed greatly to academic pharmacologists). "There are just not enough clinical investigators in this country to carry out all the studies that will be demanded of the pharmaceutical companies", CIBA Research Director George de Stevens told the National Association of Science Writers in 1970 (REF. 10).

So, the Psychiatry Panel sat down to consider the evidence. It was to make judgements on the basis of firm scientific data; namely, well-controlled, double-blind trials. However, because such trials on psychopharmacological products had started only around 1955, few drugs had a dossier of this kind of evidence available. And the trials that had been done were often underpowered and based on clinical populations that were anything but homogeneous. Nonetheless, the Panel accepted negative evidence from these trials as convincing proof of inefficacy. For example, they found captodiame (Ayerst's Suvren; Lundbeck's Covatin) less than effective[11], mainly on the negative evidence of one controlled crossover trial in 17 restless elderly patients — a notoriously heterogeneous population[12] — while ignoring two quite enthusiastic reports available to them that also had small numbers of patients, but had good results[13,14].

The Panel waved through many of the drugs with which the psychiatrist members had working familiarity; namely, the few tricyclic antidepressants then on the market and several phenothiazine antipsychotics. However, as remarked, most psychopharmaceuticals were prescribed by family doctors and internists in primary care, not by asylum- and university-based psychiatrists, and the panelists had little direct experience with 'antineurotics', to use a term current in those days, meaning the drugs for community anxiety and depression that had started to become available with the arrival of meprobamate in the mid-1950s.

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Some of these withdrawn drugs did genuinely deserve their fate, as it is clear from both qualitative and quantitative evidence that they had little efficacy and that many indications were handed down from another era. Butabarbital, for example (although not withdrawn), had been indicated for 'simple hysteria'[15]. However, several antineurotic drugs were rejected primarily because no controlled trials of efficacy had been undertaken for them. But there is other evidence, such as extensive open-label studies, that some of these drugs were indeed efficacious and did not merit withdrawal. Today, these compounds have been largely forgotten.

This paper considers some of these drugs, and the 'naturalistic' (experience-based) evidence for their efficacy, from the viewpoint of drug discovery today. It is not proposed to revive these drugs, which are now long off patent, but rather to encourage other researchers to study their receptor profiles in the hope of identifying patentable compounds that are now on the shelf — or are capable of being synthesized — with similar profiles.

Baby out with the bathwater

Ultimately, 48.5% of psychiatry drugs on the US market were withdrawn by the FDA, almost entirely as a result of the recommendations of the Psychiatry Panel (TABLE 1): fully half of the US psychiatric pharmacopoeia was found to be less than effective. Among the categories to suffer most grievously were combination products, such as Carter-Wallace's Deprol, a mixture of meprobamate and benactyzine[16]. But among the single-compound products, hardest hit were the antineurotics. The FDA ultimately withdrew 13 of the 18 antineurotics that were assessed by the Psychiatry Panel (FIG. 1). Were all of these rejected drugs truly so lacking in efficacy?

There is evidence that with some of the antineurotics, at least, the Panel 'threw the baby out with the bathwater'. For example, the five members found Wyeth's Spartase tablets to be only possibly effective, which meant the drug would have to be withdrawn within six months unless the company provided convincing proof of efficacy[17]. Spartase, a mixture of potassium aspartate and magnesium aspartate, was first marketed in 1961 as an antifatigue agent, and Wyeth was said to have big plans for the compound, which was

Table 1 | **Psychiatry drugs evaluated by the NAS/NRC Psychiatry Panel***

Type	Total number considered by the Panel	Number later withdrawn	% Withdrawn
Antineurotics	18	13‡	72.2
Antipsychotics	13	2	15.4
Barbiturates	4	0	—
Stimulants	9	1	11.1
MAOIs	3	1	33.3
Tricyclic antidepressants§	2	0	—
Combination drugs	19	16	84.2
Totals	*68*	*33*	*48.5*

*The drugs were evaluated between 1966 and 1968, and were subsequently withdrawn by the FDA in the years 1968–1974. ‡Includes buclizine, admitted as effective for nausea but psychiatric indications withdrawn. §Imipramine, amitriptyline. FDA, US Food and Drug Administration; MAOIs, monoamine-oxidase inhibitors; NAS, National Academy of Sciences; NRC, National Research Council.

proposed by some to be a potential drug for male sexual dysfunction[18], before the FDA forced its withdrawal in 1970 (REF. 19).

The generic aspartate salt combination has since enjoyed huge success in alternative medicine. A recent search on Yahoo! for 'magnesium potassium aspartate' produced 9,320 hits, many concerned with chelation therapy and chronic-fatigue syndrome.

What is the evidence for the efficacy of aspartate as an antineurotic? Palma Formica, a family physician in Woodbridge, New Jersey, who characterized 'housewife's syndrome', did a single-blinded crossover trial versus placebo with 26 patients in her practice who complained of vague somatic symptoms plus fatigue. There was no drug effect in any of the placebo periods — indeed, she could scarcely convince the placebo patients to continue — but 87% of the active-treatment patients had a positive response. "The change was startling in the patients who responded", she reported, "They had become alert, cheerful, animated and energetic and walked with a lively step. They stated that sleep refreshed them as it had not done for months … Morning exhaustion had completely subsided"[20]. These are actually quite impressive results, although the sample size and conduct of the research fall short of the FDA standard. (No wonder that the Psychiatry Panel sniffed at it as having "serious errors in design".) But the aspartate salt combination seemed to have some kind of therapeutic effect. What receptor profile did it have?

The Psychiatry Panel was dubious about Merck's emylcamate (Striatran), and bridled at the company's claim that it might be suitable for anxiety and tension: "The Panel is not sure what is meant by 'anxiety and tension occurring alone'"[21]. Emylcamate was a carbamate, the patent for which Merck had acquired in 1912. The substance was considered effective enough for the A/B Kabi Company of Stockholm to take out a Swedish process patent in 1957 and a US patent in 1961 (REF. 22). Merck began to market emylcamate in 1960 as "a new, improved, potent relaxant for anxiety and tension", superior to meprobamate[23], which at the time, just one year after the launch of chlordiazepoxide (Librium), still dominated the anxiolytic market.

The evidence for emylcamate's efficacy? Among other studies, in Philadelphia, Harry Shubin and Nathan Steinberg did a semi-controlled investigation of 400 patients in a general office practice and an in-patient setting who had a range of diagnoses, from psychoneurosis to psychosis[24]. The study had three arms: emylcamate, meprobamate and placebo, but they discontinued the placebo after the fiftieth patient and did not tabulate the placebo results, because the patients so quickly recognized that they were on it. Among the 324 patients who had psychoneurosis, 72.3% had a good or excellent response compared with 64% of those on meprobamate. Few of the psychotic patients responded to either drug. The authors concluded: "Emylcamate is an effective drug for the treatment of anxiety states"[24]. Again, in its lack of scales and premature interruption of the placebo, this is not a study that would clear the FDA bar. However, it indicates that the drug had something to offer, and it would be interesting to learn its receptor profile.

One final drug among the 13 withdrawn antineurotics might be worth scrutiny today: hydroxyphenamate, a carbamate patented in 1962 by Armour Pharmaceutical and marketed already a year previously, in 1961, as Listica, "the first selective tensitropic"[25].

The evidence on behalf of hydroxyphenamate? There are some mildly interesting quantitative data, which the Psychiatry Panel

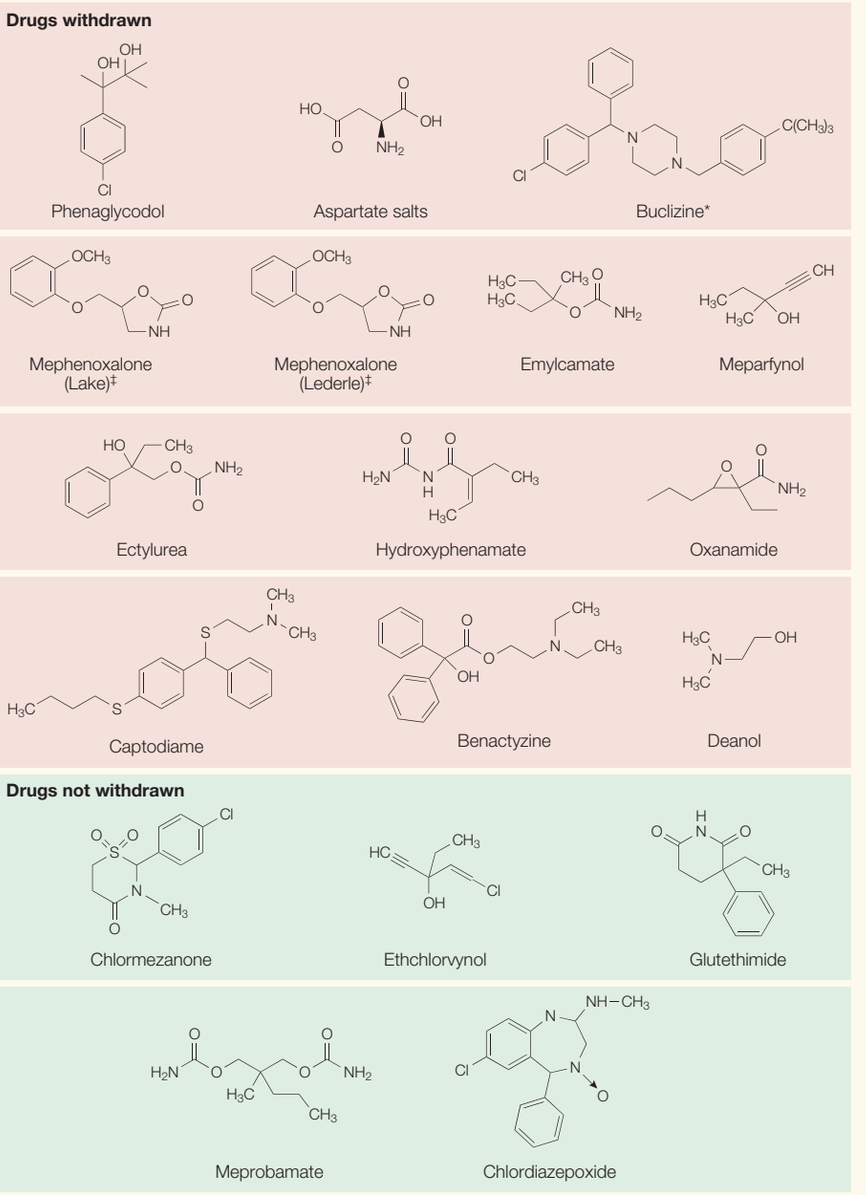

Figure 1 | **Antineurotic drugs evaluated by the NAS/NRC Psychiatry Panel, 1966–1968: 13 out of 18 were subsequently withdrawn by the FDA.** A compound with indications that received not a single 'effective' rating would be withdrawn. *Buclizine admitted as effective only for nausea. ‡Different companies (Lake and Lederle) offered mephenoxalone for different indications, and the evaluation of the Psychiatry Panel was by indication, not by compound as a whole. FDA, US Food and Drug Administration; NAS, National Academy of Sciences; NRC, National Research Council.

dismissed as coming from "a symposium arranged by the sponsoring company"[26] (if all such evidence were dismissed today, psychopharmacology would cease to exist). At the symposium, Blaine McLaughlin and collaborators presented evidence from a three-arm crossover study involving Listica, Librium (chlordiazepoxide) and placebo on outpatients at the Psychiatry Clinic of the Woman's Medical College in Philadelphia. Twenty-four patients completed the trial. In the Listica phase, 18 of the 24 responded well; 19 of 24 responded well in the Librium phase and 9 of 24 responded well in the placebo phase[27].

The qualitative data — the testimonials at the company-sponsored symposium at which these results were presented — are even more interesting. Edward Greenspan, a cardiologist at New York Medical College, felt the drug helped his hypertensive patients to relax: "I have tried Librium. I have tried nialamide and Tofranil (imipramine). I don't find good results with people above 55 and 60. I don't find the monoamine oxidases help me as much as a tranquilizer of this type"[28]. According to Leo Alexander, a well-known Boston psychiatrist and specialist in physical therapies: "Perhaps the greatest advantage of the drug is its mildness. There is no other drug that has these effects, except benactyzine"[29].

These comments and paltry statistics do not, of course, represent definitive proof of the efficacy of hydroxyphenamate. But they suggest that a second look might be worthwhile: the drug clearly was doing something, and if its mechanism of action could be identified, drug discovery in psychopharmacology might be moved forward.

Discussion

It is clear in retrospect that several of the drugs that were discarded by the Psychiatry Panel might have been effective. The Pharmaceutical Research and Manufacturers Association made this point for the NAS/NRC Review as a whole, which witnessed a veritable slaughter of the innocents among US pharmaceuticals: "Many products placed in qualified categories were actually considered by members of the panels to be effective … In many cases, a labelling modification, not the effectiveness of the medication, was in question"[30]. Daniel Freedman, head of the Psychiatry Panel, agreed that the Panel had gone overboard in its insistence on controlled trials as a precondition for keeping drugs on the market. He told Congress, "There are some very good [psychotropic] drugs backed up by very little objective data". He suggested that it was "up to FDA" to implement with caution the recommendations of the Panel[31].

There is a lesson for our own times about over-reliance on controlled trials. Good anecdotal data, or solid data from open-label trials, do not automatically constitute 'testimonial evidence', much feared in modern pharmacology as a residue from an era when bearded frontier physicians hyped codeine-laced cough syrup. As Alvan Feinstein, the noted McMaster University epidemiologist, told a seminar on the Philosophy and Technology of Drug Assessment in 1972: "We have boxed ourselves into a rigid methodological approach for evaluating any kind of therapy … We are going to be in terrible trouble … as long as we continue to delude ourselves into thinking that utilizing the double-blind randomized approach is our only concern. Until we realize that all of these important humanistic data are being deliberately ignored, inadvertently neglected, or not properly assembled and analysed, we will continue to engage in a dehumanized form of pseudoscience"[32].

The pharmacologist Louis Lasagna, mindful of the misadventures of DESI, added to this discussion: "I am not willing to throw out a lot of naturalistic experience on the basis of one or two negative double-blind trials. I have seen too many negative double-blind trials"[32].

Other distinguished academic investigators made similar criticisms of the NAS/NRC audit and the unrelenting application of its results by the regulators of the FDA. The evidence on behalf of the drugs discussed in this paper is considerable, albeit not in the form of controlled trials. Their mechanism of action deserves a second look, in the hope of developing truly effective pharmaceuticals to treat mood and anxiety disorders.

In conclusion, the past is a great warehouse of compounds of potential use for the future of psychopharmacology. Many other drugs that were synthesized in the United States and Europe in the first half of the twentieth century and were then forgotten — drugs far off the screen of the NAS/NRC Drug Efficacy Study — offer promise of efficacy. At a time when literally billions of dollars are being poured unsuccessfully into the discovery of new psychoactive compounds, it would be a shame if some of these fading beauties were not re-examined to see how they worked.

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doi: 10.1038/nrd964

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Online links

FURTHER INFORMATION
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National Association of Science Writers: http://nasw.org/
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