Making the First Anti-Depressant: Amphetamine in American Medicine, 1929–1950

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We are accustomed to thinking of the widespread use of anti-depressant drugs as a recent phenomenon, and one of decidedly mixed blessings. While no doubt effective, their phenomenal popularity since the 1990s has raised questions about the medicalization of problems of living and the fading boundaries between healing and medical enhancement (or the specter of “cosmetic pharmacology,” in Peter Kramer’s pithy formulation). Today’s anti-depressants have also, for some critics, come to symbolize the excessive influence of the pharmaceutical industry over the definition and treatment of illness. Drug companies are said to reshape, or even invent, disorders to fit the drugs they are marketing, manipulating medical knowledge like never before—and particularly in the area of mental health. The historical narrative that often underpins such critiques places the beginnings of psychiatric medicine’s loss of control over pharmaceuticals around 1960, when the monoamine oxidase inhibitors and (especially) the tricyclic anti-depressants first entered the market. A variant narrative suggests that, instead, it was...

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Miltown and the other minor tranquillizers that ushered in widespread pharmaceutical influence over psychiatric thinking and practice, during the second half of the 1950s. In either account, society today is portrayed as overmedicated for depression and other functional psychiatric disorders because the boundaries of illness have been overstretched by drug company marketing, and sound professional judgment no longer governs prescribing.

This article will argue that such accounts abbreviate and oversimplify the longstanding and complex interplay between psychiatry and the drug industry. In particular, they ignore an earlier period, beginning in the late 1930s, when amphetamine was widely used as a specific therapy for neurotic depression. Here I attempt to recover this forgotten early chapter, in order to show that amphetamine represents the first of the anti-depressant drugs, even though it was invented for another purpose and is no longer regarded as an anti-depressant. Indeed, the introduction of amphetamine to psychiatry in the 1930s and 1940s played a key role in reshaping medical understanding and practice, along with popular expectations, to create a society of psychiatric outpatients routinely consuming mood-altering drugs en masse. That is, amphetamine established the need—the market—for anti-depressants that a succession of later drugs, including the currently dominant selective serotonin reuptake inhibitors (SSRIs, e.g., Prozac), have filled since. Furthermore, medical thinking about depression and its treatment appears to have been influenced by the drug industry, in this earlier period, in much the same manner that it is said to have been influenced in later years. Thus, the story of amphetamine’s


development as an anti-depressant opens large questions about the ways we think about both the history of pharmaceuticals and the history of depression.

THE HISTORIOGRAPHY OF PSYCHIATRY AND THE PSYCHIATRIC MEDICINE OF INTERWAR AMERICA

Unfortunately, the standard historiography of psychiatry presents major obstacles to interpreting the story at hand and therefore must be addressed at the outset. According to the current standard narrative, biological psychiatry in the 1960s was a new and revolutionary force that by the end of the next decade had overthrown a thoroughly psychoanalytic establishment, in place since before World War II. Before this “biological revolution,” psychoanalysis and other “dynamic,” talking approaches had little to do with psychiatry as practiced in mental institutions. Freudian therapists believed that most if not all mental illness could be healed through insight into the distressing early experiences that had caused it. Thus they eschewed the use of drugs for all but the most hopeless psychoses, just as they scorned lobotomy and electroshock and other biological therapies; outpatients being treated for neurotic conditions largely shared the same aversion to drugs. For their part, the institutional psychiatrists were more biologically inclined in their approaches to their seriously ill inpatients, but they saw drugs as nothing more than sedatives and instruments of restraint (at least until the mid-1950s’ introduction of antipsychotic agents like chlorpromazine). Only after a more biological perspective spread from institution-based psychiatry in the later 1960s, reinforced with newly effective drugs like the tricyclic antidepressants, was Freudian talking therapy put into retreat and the way paved for the biological understanding—and drug treatment—of common, relatively minor psychiatric conditions.3 There is no place in such a narrative for an anti-depressant drug to have been developed

in the late 1930s and to have achieved wide success as a specific therapy for depressed outpatients in the 1940s and 1950s. Nonetheless, as I shall argue here, there was such a drug, and it was amphetamine.

Though this article is by no means an adequate vehicle to develop a new historiography of psychiatry from whole cloth, it does point toward an alternative perspective already suggested by recent historical work. According to this alternative view, we must regard psychiatric medicine in the United States as more diverse and eclectic, and less polarized, than any scenario placing a long struggle between psychoanalysts and biological psychiatrists on center stage. For instance, Jonathan Metzl has shown that minor tranquilizers, represented as aids to talking therapy, were marketed with apparent success to Freudian psychiatrists in the 1950s and 1960s. The same was done with amphetamine, as we shall see. Thus a psychoanalytic approach was not inconsistent with psychiatric drug prescription—although in such situations the drugs were thought of as acting on anxiety symptoms without affecting the neurotic illness itself. Similarly, Jonathan Sadowsky has found that many Freudian psychiatrists were accepting of electroconvulsive therapies in the early postwar period and were easily able to accommodate their effectiveness within psychoanalytic theory. Another very important insight has come from recent work by German Berrios and collaborators, who have looked at the disjunct between specialist psychiatry and primary care with respect to psychiatric diagnosis and treatment. From the early twentieth century to the 1980s, Berrios observes, expert opinion in psychiatry was highly discordant as to the nature of depression and its proper treatment, leaving the general practitioners—who actually prescribed (and still prescribe) over 85% of all psychiatric drugs—free to treat their emotionally distressed patients with barbiturates, minor tranquilizers, tricyclic antidepressants at placebo doses, or whatever other therapy they thought might bring symptomatic relief. It is easy to see how amphetamine, which was widely marketed to general practitioners for treatment of mild depression from the 1940s to the mid-1960s, fits with this picture.4

Most important may be the work of Jack Pressman on the complex and eclectic state of American psychiatry in the 1930s and 1940s, the context in which amphetamine emerged as the first anti-depressant. As Pressman has argued, in the United States, the period between World War I and World War II was one in which the previously distinct worlds of the isolated asylum psychiatrists and the elite neurologists, who advised affluent outpatients in comfortable urban consulting rooms, were united in a new field of “neuropsychiatry.” This inclusive American vision of mental medicine, largely conceived and constructed by Adolph Meyer and his followers, saw the medical approach to psychoses in asylums, the dynamic theories and talking therapies of the Freidians with neuroses, laboratory experiments in nerve physiology, and even empirical sociology all as valuable perspectives that could be brought to bear on the problem of human “psychobiology” in a coordinated fashion. Distinctions between physical and mental, between physiological and social, and between insanity and problems of living were deliberately broken down in an effort to create a medical discipline taking “disorders” of individual “adjustment” as its domain. Pragmatic and eclectic, and enjoying the support of powerful philanthropies that saw a discipline of the mind based firmly in scientific medicine as the solution to America’s social problems, this new neuropsychiatry was firmly established in the 1920s and 1930s at influential medical schools such as Harvard and the University of Pennsylvania. Nor was the ecumenical attitude restricted to specialists trained at these elite psychiatric centers; in standard general-medicine textbooks one finds Freud treated as just one contributor among many to the medical understanding of mental illness. Meyer remained influential with his own views about the instinctive drives and their channeling in the course of life history, emphasizing conscious adaptive mechanisms rather than the unconscious ones stressed by strict Freidians, and with his own approach to talking therapy as well. Because it treated mind as embodied, American (neuro)psychiatry was open to a wide range of somatic approaches in the interwar period, embracing such innovations as malarial therapies, insulin coma, electrical and chemical convulsion, and psychosurgery or lobotomy, especially for treating more severe, psychotic illnesses (which were, however, typically regarded as differing from related neurotic disorders only in severity but not in kind). Mindful of this context, one will find it less surprising that a specific drug treatment
for milder (neurotic) depressions should find a receptive audience in the 1930s.\footnote{5}

**THE INVENTION OF AMPHETAMINE**

Although amphetamine would find its first important medical uses in psychiatry, the path by which it was discovered shows no early sign of leading in that direction. This synthetic drug emerged from the drive to make pharmaceutical products based on hormones, and in particular on adrenaline. The adrenal gland was one of the first organs identified as a source of “internal secretion” or hormones, along with the thyroid and testes, in the earliest days of endocrinology. By the 1890s the action of the adrenal hormone on various tissues and processes had become a major focus of experimentation among physiologists, while the identification of this blood pressure-raising substance had become a competitive field among biochemists. Soon, a number of relatively pure adrenal extracts had been prepared, each highly active in raising blood pressure, and a number were marketed by drug firms. But the product trademarked as “Adrenalin,” prepared by chemist Jokichi Takamine and marketed by Parke, Davis and Company beginning in 1901, quickly came to dominate the market.\footnote{6}
Because it caused capillaries to constrict and thus restricted local blood flow, surgeons embraced the hormone drug enthusiastically as a hemorrhage-reducing additive with local anesthetics. The blood pressure–raising (“pressor”) power of an adrenaline injection made it a useful treatment for shock, and the hormone’s relaxing effects on the bronchial passages quickly made it essential for the treatment of asthma. In the wake of its commercial and clinical success, some chemists sought other drugs with “sympathomimetic” action (so called because adrenaline’s wide range of actions in general mimic the effects of stimulation of the sympathetic nerves to each particular organ and tissue, causing the smooth muscle of the intestine to relax, tear gland secretion to be boosted, pupils to dilate, etc.). Most notably, physiologist Henry Dale and chemist George Barger at the Burroughs-Wellcome firm in Britain systematically generated dozens of synthetic compounds structurally related to adrenaline, finding one with a longer duration of action in its pressor effect; it was eventually marketed by the firm for shock under the brand name Tyramine, albeit without huge commercial success.7
The next important sympathomimetic to reach the medical market was ephedrine, discovered in the traditional Chinese herb Ma Huang, or *Ephedra vulgaris*. Japanese scientists were the first to purify, characterize, and commercialize the drug, but its discovery for Western medicine came from US-trained scientists Ku Kuei Chen and Carl Schmidt at Peking Union Medical College in 1923. Like the structurally similar adrenaline, ephedrine was found to raise blood pressure, though not powerfully enough to replace Adrenalin and Tyramine as medicines for the treatment for shock. Its capillary-constricting effect, though much longer lasting than that of adrenaline, also proved insufficient for the drug to replace Adrenalin as a surgical hemorrhage preventive. However, this capillary-constricting effect is strong enough to shrink swollen nasal tissue, providing hours of congestion relief when applied by spray or taken as a pill, and the drug became enormously popular with cold and allergy sufferers soon after it was introduced to the market by the Lilly firm in 1926. Furthermore, ephedrine is also somewhat effective in relaxing bronchial passages, though less so than adrenaline. But since it is active when taken orally, it quickly became popular among asthmatics, who would take it to forestall attacks (though an adrenaline injection was still needed if an attack did occur). Ephedrine and the related compound pseudoephedrine could be synthesized, but the most economical source of supply remained Ephedra plants grown in China, and Lilly controlled most of the Chinese production.\(^8\) Supply of ephedrine was short, and prices high, in the late 1920s, so for the enterprising there was a great incentive to find a substitute decongestant and asthma reliever.

This demand for an ephedrine substitute was the impetus behind the development of amphetamine, together with an exuberant overall atmosphere in the business of drug development during the 1920s.

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The pharmaceutical industry had recently begun looking hard for new scientifically legitimate products, having been disciplined by medical reformers to justify advertising claims with scientific evidence. Close collaborations were formed between drug firms and some of the leaders in biomedical research, especially in the fast-moving and competitive fields of endocrinology and vitamin research. Vitamin D, insulin, and a host of other new laboratory discoveries quickly found their way to medical practice in the 1920s, thanks to a veritable frenzy of industrial-academic collaborations that one contemporary endocrinologist described as a “gold rush.”

Southern Californian Gordon Alles received his formation as a biochemist amid this entrepreneurial atmosphere. Alles’s 1924 masters thesis at the California Institute of Technology dealt with the chemical properties of insulin, particularly with ways to quantify it in vitro and thus to standardize doses, and also its possible mode of action. He began working in the large practice of Los Angeles allergist George Piness, making protein preparations for allergy desensitization treatments, while continuing in a doctoral program at Cal Tech. His 1926 Ph.D. thesis dealt with physiological effects of some novel chemicals he had derived from guanidine, particularly their effects on blood pressure, respiration, and blood sugar in rabbits; in this, Alles appears to have been seeking a synthetic substitute for insulin. In 1927 to 1928, Alles spent an
academic year getting a taste of drug company–academic collaborations as a postdoctoral fellow in the Harvard laboratory of Edwin Cohn, then deeply involved with Lilly in a project to develop a pernicious anemia drug from liver extract.\textsuperscript{11}

Unable to land an academic job, Alles returned to his job making desensitization preparations in Los Angeles and also researching new allergy drugs. One new sympathomimetic that he worked with was phenylethanolamine, useful in nose drops, but lacking ephedrine’s prized oral activity. Seeking whatever it was that made ephedrine able to withstand the stomach long enough to enter the blood, Alles prepared some more molecules related to ephedrine and soon took a special interest in one of these, phenylisopropylamine—phenylethanolamine with ephedrine’s extra carbon added to the side chain (and with the side chain hydroxyl group removed). Prepared as the sulfate salt, in animal tests it was active by mouth like ephedrine, had a pressor effect much longer lasting than adrenaline, and was not terribly toxic.\textsuperscript{12} So, in early June 1929, Alles tested this chemical, which I will from now on call “amphetamine” for simplicity (though it would not receive this name officially for almost ten years), on himself. He noted a “feeling of well being,” “palpitation,” and eventually a “sleepless night” in which his “mind seemed to race from one subject to another.” Two days later the chemical was given to the first of several of Dr. Piness’s patients undergoing an asthma attack. It proved a mediocre asthma remedy, but these patients also experienced “exhilaration” and “palpitation”—that is, central nervous system and cardiac effects. In July 1929, Piness presented the group’s results of trials with their phenylethanolamine decongestant at an American Medical Association meeting in Oregon and also their first findings on the treatment of asthma and hay fever with amphetamine.\textsuperscript{13}

\textsuperscript{11} Alles to Piness, 22 October 1927, folder “Originals—1927,” box 14, GAP. Alles to Piness, 24 February 1928, Hyman Miller to Alles, 29 February 1928, and Alles to Piness, 6 March 1928, folder “Originals—1928,” box 14, GAP. On the Harvard-Lilly collaborations, see Swann, Medical Scientists, ch. 5; Alles to Piness, 24 February 1928, folder “Originals—1928,” box 14, GAP.


\textsuperscript{13} Ibid., 12–14. For animal experiments, see also e.g. Alles, 27 November 1928, “Exp. #2”; Alles, 1 December 1928, “Experiment 6”; Alles, 10 April 1932, untitled experiment on “Dog, 9 kg”; for human tests, see e.g. Alles, 3 June 1929, “B-Phenyl-isopropyl amine
Though Alles filed a patent on amphetamine in the form of sulfates and other salts, there was no celebration over the drug, and for the next four years his research efforts were mainly devoted to finding a synthetic, orally available asthma and allergy remedy superior to ephedrine—preferably without the stimulatory side effects. Starting in 1931, he began conducting some of the animal work associated with his research at the pharmacology department of the University of California medical school in San Francisco (UCSF), an association that continued for many years. Meanwhile, Alles looked for ways to make something of his failed asthma drug. In 1933 he supplied some amphetamine to Myron Prinzmetal, who as a medical student had worked with him at UCSF, to try out in narcoleptic patients in St. Louis; if the self-experiments had not made this idea obvious, some recent reports that ephedrine was beneficial for the disorder would have. That year Alles also supplied Morris Nathanson, a Californian physician then working in Minneapolis, with amphetamine to test as a heart stimulant, along with ephedrine and adrenaline. Nathanson too tried the drug on narcoleptics, with some success, and then carried out a trial on forty patients complaining of fatigue and asthenia. Alles also supplied some to another UCSF alumnus, S. Anderson Peoples, who wanted to try it on psychiatric patients during his fellowship at London’s Maudsley Hospital, and to Michael


Leventhal, a Chicago gynecologist who wished to try the drug for dysmenorrhea (premenstrual cramps and/or painful menstruation). Thus did the process of clinical development haphazardly begin, in which (to use Rein Vos’s memorable phrase) a “drug looking for a disease” may find its place, and at length become an important medicine. There was no plan to make amphetamine an anti-depressant, nor to find any use for it among neuropsychiatrists—nor even to define amphetamine’s stimulating central nervous system “side” effects as the drug’s chief action. As we shall see, in the case of amphetamine, the process of finding this groundbreaking use seems to have had two distinct phases. First, the major drug firm with which Alles soon allied himself cast its net more broadly and systematically, using an extensive network of clinical collaborators to test the waters for amphetamine in a wide range of medical specialties. Then, after ruling out several unrelated, potentially lucrative possibilities and identifying a significant interest among neuropsychiatrists, the firm focused both its sponsorship of research with the drug and its marketing efforts (which were not always clearly distinguishable) on defining and promoting uses of the drug for that specialty. The use that caught on among neuropsychiatrists was for therapy of common, milder depressions, and it spread to general practice. Although medicine might on its own have arrived at the same outcome, one can never know what would have become of amphetamine if the pharmaceutical industry had not played such an active role in its clinical development.

THE DRUG FIRM AND THE SEARCH FOR CLINICAL DEMAND

While Alles was beginning to test his invention through his own, informal network of clinical researchers, a new drug dubbed “Benzedrine” was released on the market by the Philadelphia firm Smith, Kline and French (SKF). Benzedrine was the same compound as Alles’s—phenylisopropylamine, that is, amphetamine. SKF chemist


Fred Nabenhauer had developed the drug in the form of a volatile free base rather than the orally active salts that Alles had patented; although he might have discovered it independently (as the firm would claim), this is doubtful, given that Alles’s first presentation on amphetamine at the 1929 AMA meeting in Oregon seems to have been reported promptly to SKF management. However the firm happened to discover the drug, SKF first packaged it as an inhaler so as to exploit the base’s volatility and, after sponsoring some trials by East Coast otolaryngological specialists, began to advertise the Benzedrine Inhaler as a decongestant in late 1933.\textsuperscript{17} By April 1934, Alles had approached both Merck and SKF, and in December he reached agreement with SKF, assigning the firm the patent in exchange for 5\% royalties on sales of Benzedrine salts.\textsuperscript{18}

Alles had found a strong ally for the commercial development of amphetamine in Smith, Kline and French. The firm had just come under dynamic new leadership in the form of Frank Boyer and W. Furness Thompson, who aimed to move SKF away from nerve tonics and dandruff remedies into the arena of science-based pharmaceuticals. Though not the scientific powerhouse that some leading American firms like Merck and Lilly had become by the mid-1930s,


\textsuperscript{18} Alles to Leake, 27 April 1934, folder “Correspondence Not Listed in Card File,” box 16, GAP. Francis Boyer to Alles, 5 June 1934; Alles to Boyer, 26 June 1934; Boyer to Alles, 6 July 1934; Alles to Boyer, 1 August 1934; all in folder “Sale of Invention and Patent 1,879,009 on Benzedrine Salts as Medicinal Agents,” box 1, GAP. Alles to Boyer, 8 September 1934; Boyer to Alles, 17 September 1934; Alles to Boyer, 25 September 1934; Boyer to Alles, 22 October 1934; Alles to Boyer, 12 November 1934; Boyer to Alles, 6 December 1934; Alles to Boyer, 17 December 1934 and attached contract; all in folder “Sale of Invention and Patent 1,879,009 on Benzedrine Salts as Medicinal Agents,” box 1, GAP. See also Ted Wallace memo, 8 November 1935, unlabeled folder, box 15, GAP.
the firm stood among drug industry leaders in marketing sophistication and innovation, including the use of science in marketing.\textsuperscript{19} This was a time of profound change in the American pharmaceutical industry. A reforming medical elite had managed to impose some measure of voluntary discipline on manufacturers during the first two decades of the century, for instance barring companies from advertising prescription drugs directly to the public, and requiring a drug’s approval by the AMA’s Council on Pharmacy before it could be advertised to the medical profession in the \textit{Journal of the AMA (JAMA)} and other cooperating journals. Thus, by the mid-1930s, “ethical” drug firms (those that followed the reformist rules) were largely limited to advertising in medical and scientific journals, plus direct marketing to physicians using their growing sales forces of “detail men.” Now that science was required to win approval to advertise drugs, the scientific literature itself became a key arena for drug marketing. Of course, the citation of medical articles in advertising copy and the distribution of journal offprints by salesmen were not new practices, and neither was sponsorship of some research by drug firms.\textsuperscript{20} But by the 1930s, leading firms like Smith, Kline and French had learned to involve themselves in the medical research literature to a remarkable extent, from conceiving and designing clinical studies that targeted particular medical audiences, to overseeing their execution by competent or even eminent researchers, to managing their writing, illustration, and publication in top journals.\textsuperscript{21}

When Alles began mingling with the SKF management teams handling new drug development in early 1935, the firm’s top priority was improving its recently launched Benzedrine Inhaler’s share of the decongestant market. Alles observed as SKF organized studies by clinical researchers aimed at producing scientific literature that would show the Inhaler to be beneficial in new ways and thus justify medical advertising claims. For instance, respected occupational hygiene researcher Howard Diehl of the University of Minnesota was attempting

\textsuperscript{19} Mahoney, \textit{Merchants}, 33–35.


to prove for the firm that the Inhaler could “abort” or prevent incipient colds, and pediatrician Joseph Stokes of the University of Pennsylvania was funded for a study to test the Inhaler on children of various age groups.\footnote{On sales, see memo from “Mister Valentine,” 15 February 1935; on Diehl, see Wallace memo of 20 June 1935; on Stokes, Wallace memos of 5 September 1935 and 6 December 1935; on progress of both studies, Wallace memo, 3 August 1937; all in unlabelled folder, box 15, GAP. Also on Stokes, [anon.], SKF Research Program (# 18), 8 June 1938, folder “SKF v. Alles documents received from Alles Office,” box 2, GAP.} The firm’s medical research staff designed protocols and sometimes outlined in advance the research articles to be written, once results were obtained, for some of these researchers. For example, Philadelphia rhinologist Joe Scarano, one of the clinicians who did an early trial comparing ephedrine and Benzedrine as topical decongestants to help win AMA approval of the drug, was engaged to follow up with articles showing that the Inhaler caused no harmful changes in nasal tissue and no problems for use in children and even infants. This office practitioner was clearly one of the firm’s regular stable of clinical investigators, but so too were distinguished medical authorities like University of Pennsylvania pediatrician Joseph Sulman, similarly engaged by SKF.\footnote{On Sulman, see Wallace memo of 5 September 1935; on Scarano, Wallace memos of 7 February 1935, 28 February 1935, 9 May 1935, and 6 December 1935, all in unlabelled folder, box 15, GAP. See also Joseph Scarano, “Rapidity of Shrinkage;” idem., “Gross Changes Produced in the Nose by Benzedrine Inhalation: An Analysis of 100 Cases,” \textit{Med. Rec.}, 1936, 143, 161–62; J. Scarano and J. F. Cioppolino, “The Use of Benzedrine Vapor in Children,” \textit{Arch. Pediat.}, 1937, 54, 97–100; L. D. Sulman, “Certain Conditions in which Volatile Vasconstrictor has Proved of Particular Value: A Preliminary Report,” \textit{Med. Times Long Island Med. J.}, 1935, 63, 374–75. On drug company–medical researcher collaborations in the period generally, see Rasmussen, “Moral Economy;” idem., “The Drug Industry and Clinical Research.”} Beyond merely establishing the efficacy and comparative safety of their product for AMA Council review, the firm also showed considerable finesse in using science to address a marketing problem surrounding the Inhaler’s non-prescription sales to the general public. SKF had discovered that consumers perceived the Inhaler as dangerous, largely due to druggists’ cautious attitudes—physicians’ high confidence in the product notwithstanding. Interviews with consumers suggested that removing the “Do Not Overdose” warning label on the Inhaler would help the product’s safety image. So the firm commissioned studies by academic pharmacologists and clinicians to quantify the amphetamine dosage absorbed from inhaling and to show that damage to nasal cilia would not occur from overuse of the Inhaler. Thus, removal of
the warning could be justified, and published findings on the Inhaler’s safety generated for use in advertisements.24

Around the beginning of 1936, Smith, Kline and French commissioned toxicity studies of amphetamine sulfate. University of Pennsylvania pathology professor Edward Krumbhaar found minimal harm in rats given large doses over several weeks, and an abstract of these results was written up in early 1937, mimeographed, and sent to all clinicians using the drug experimentally so that they would be reassured about its safety.25 The firm was already distributing 10 mg tablets of amphetamine sulfate and identical placebos for experimental use to Alles’s physician contacts such as Nathanson, as well as to other clinical researchers engaged by the firm. For instance, University of Pennsylvania Internal Medicine professor Wallace Dyer was funded to study its effects on blood pressure in wider patient populations, in order to see whether the drug might be useful—or dangerous—in people with high or low blood pressure. But apart from these company-commissioned and –designed trials, there were also many by freelancers, to whom the firm only supplied drugs in exchange for regular updates on results.26 Once word of Prinzmetal’s studies on narcolepsy began to spread, by mid-1935, neurologists and psychiatrists in particular approached SKF with inquiries and requests for the drug. After the narcolepsy paper appeared at the end of the year, the firm began marketing the drug for that condition.


However, SKF wanted to establish a broader range of indications for the drug before they would apply for full AMA Council approval, waiting to accumulate further findings that would justify much broader advertising claims.27

Physician acceptance of Benzedrine Sulfate for treatment of dysmenorrhea would have guaranteed the new drug a huge market, for this complaint was the “bete-noir of the gynecologist”—extremely common and otherwise untreatable. But hopes for this profitable outcome, plausible on the grounds that the drug blocked uterine contractions in certain experiments, gradually slipped away when promising clinical findings were not substantiated physiologically.28 So too did hopes that Benzedrine would be more useful for hay fever than it was for asthma. Like the trials showing the Inhaler to be ineffective in aborting colds, these findings seem mostly to have remained unpublished, as was typically the case with unfavorable company-sponsored studies.29 However, prospects for a market among neurologists and psychiatrists, building on Benzedrine’s central nervous system effects, blossomed during 1936. As noted, in American psychiatry of the 1930s, sharp distinctions were not always drawn between the psychotic conditions with which institutional psychiatrists mainly concerned themselves and the milder neurotic disorders treated by neurologists, while analytic and other psychodynamic


29. Webb to Alles, 14 July 1936, folder “SKF v. Alles documents received from Alles Office,” box 2, GAP; Wallace memo 16 July 1936, unlabeled folder, box 15, GAP. On non-publication, see Rasmussen, “The Drug Industry and Clinical Research.” An Index Medicus search for publications authored under the names Leventhal and other investigators engaged to study the dysmenorrhea and hay-fever indications did not lead to the discovery of any papers reporting negative results described in company correspondence (although Hundley, Krantz, and Tibbets, “Dysmenorrhea,” is lukewarm on the possible indication). Similarly, Diehl had by June 1937 informed SKF of his finding that the Inhaler was of no value in the prevention or “abortion” of colds (Wallace memo, 3 August 1937, unlabeled folder, box 15, GAP), and I find no mention of Benzedrine’s efficacy as a cold preventative in any of Diehl’s publications listed in Index Medicus, 1935–1939.
therapies mingled with innovative physical interventions such as convulsant and coma therapies.\textsuperscript{30} Drug therapies represented another promising avenue in this context. The neuropsychiatry market’s promise was obvious in March 1936: “If we haven’t got a bearcat by the tail then I’m a Dutchman,” reported one SKF observer at a Boston psychiatry meeting. The meeting had featured the debut of new work by Alles’s friend Prinzmetal on the beneficial effects of Benzedrine Sulfate on certain forms of Parkinson’s disease. More importantly, Boston neurologist and psychiatrist Abraham Myerson had reported three studies there, two of them on Benzedrine’s effects on the autonomous nervous system, and one on the drug’s effects on mood in “normals” and outpatients. In “certain depressed neuroses” where subjective symptoms are worst in the morning, the drug was “definitely ameliorative,” although not curative, according to Myerson.\textsuperscript{31} Although he was well funded already, SKF quickly began funding Myerson, who appears to have become interested in Benzedrine Sulfate on his own initiative. His enthusiasm, facilities, and standing would soon make him a champion of the product and a key asset for SKF in its efforts to create a psychiatric niche for amphetamine.\textsuperscript{32}

**ABRAHAM MYERSON AND THE NEUROPSYCHIATRISTS**

Myerson was a very eminent man indeed. Simultaneously Professor of Neurology at Tufts and of Clinical Psychiatry at Harvard Medical Schools, and also Research Director at Boston State mental hospital, he headed a lab impressively equipped for physiological work and generously backed by the Rockefeller Foundation.\textsuperscript{33} Beyond academic

30. Shorter, *History*, ch. 6; Grob, *Mental Illness*, ch. 11. See also Braslow, *Mental Ills*, although this work underestimates theoretical interest and innovative uses of drugs in the late 1930s, as compared with convulsive therapies.
32. Wallace memo, 6 December 1935, unlabeled folder, box 15, GAP.
33. Myerson to Alan Gregg, 18 June 1935, folder 872, box 72, Series 200A of Record Group 1.1 at the Rockefeller Archive Center in Tarrytown, New York (hereafter, RAC). Myerson, undated [April 1938], “Boston State Hospital—Psychiatry Annual Report March 1936–March 1937,” and Myerson, December 1939, “Boston State Hospital—Psychiatry Annual Report December 1, 1937–November 30 1938,” folder 875, box 73, RAC. See also personal correspondence, Susan Irving, RAC, 23 April 2004, to the effect that Myerson enjoyed Rockefeller research grants averaging more than $13,000 per year from 1934 through 1941.
distinction, Myerson was also a public intellectual well known for his critiques of the science behind eugenics, and for several popular books. In *The Nervous Housewife* of 1920, Myerson discussed the mounting prevalence of neuroses in American women, explaining this rise as chiefly due to the frustration by wifely social roles of instinctive drives oriented toward worldly action, together with upbringing inculcating vanity, emotionality, and unrealistic expectations from marriage. In this book Myerson showed a style typical of Meyer-influenced neuropsychiatry in interwar America, with his stress on the adaptation of the individual to social context and his insistence on the treatment of emotions as bodily, physiological states—a discovery for which he credited Pavlov and Walter B. Cannon, the Harvard physiologist famous for his studies of the psychophysical survival function of adrenaline. And although he gave a central place to instinctual drives and their repression in his psychology, Myerson was no Freudian: whereas the Viennese had hypothesized sexual traumas of early childhood as the root cause of neuroses, Myerson, like Meyer, saw no great need to look beyond recent adult experience and conditions. He recommended treating most neuroses with a combination of healthy physical conditions and diet, together with talking therapy to instill more adaptive habits and outlooks on life.34

Myerson’s popular 1925 book *When Life Loses Its Zest* had made him an authority on depression. Here he elaborated ideas on depression first proposed in 1922, when he described a depressive “symptom complex” he dubbed “anhedonia” (thus reviving and reinterpreting an obsolete nineteenth-century term, literally meaning “lack of pleasure”), which was marked by lack of interest in sleep, food, and sex, and a low level of the “energy feeling” that motivates projects in the world. Though anhedonic symptoms were common to a number of conditions, such as menopause, the early stages of schizophrenia, and recovery from surgery and infectious disease, a chronic illness he called “idiopathic” or “recurrent” anhedonia represented a distinct

neurotic disorder in its own right. Indeed, Myerson argued, this particular neurosis was reaching epidemic proportions, especially among women but increasingly among middle- and upper-class male “brain-workers.” As with the hysterias of married women he had focused upon in The Nervous Housewife, this disorder of reduced desire and pleasure could be explained as stemming from frustration of instinctual urges, particularly through the artificial overstimulation and rigorous discipline of industrial civilization. Anhedonia was best understood as a deficiency in a person’s feeling of psychic energy; indeed, although anhedonia is not always accompanied by subjective despair, “it is probable that what we call sadness is to a large extent the disappearance of the energy feeling,” Myerson speculated.35

Myerson customarily treated his private patients for anhedonia by a combination of occupational, physical, and talking therapies, all directed to restoring “pep, zeal, courage, concentration, interest,” and pleasure. First, he would establish an unstressful routine of wholesome diet and moderate exercise, coupled with an energy-restoring program of “graduated exertion” to bring the patient out of himself and into a realm of interesting and achievable goals (whether in light reading, sports such as hunting or golf, or crafts such as basket weaving). He would talk with and advise the patient, but not encourage heavy introspection; indeed, he considered Freudian psychoanalysis too introspective generally, and especially destructive for the anhedonic. And, to reestablish a regular pattern of activity and break the typical anhedonic’s cycle of insomnia, he would also treat patients with sedatives like bromides at night and stimulants like caffeine in the morning. Because mind and body were ultimately one, biological and psychodynamic approaches did not conflict for Myerson; as he wrote in 1922, “if the individual is depressed . . . you can change his attitude . . . by physical means just as surely as you can change his digestion by distressing thought . . . [D]rugs and physical therapeutics are just as much psychical agents as good advice and analysis and must be used together with these latter agents of cure.”36

36. Myerson, “Anhedonia” (quotes 91, 101); idem., When Life Loses Its Zest.
In *When Life Loses Its Zest*, Myerson not only introduced chronic lack of pleasure as a mental disease, but also proposed a major revision of standard diagnostic categories for neurosis that he had accepted in *The Nervous Housewife* (neurasthenia, psychasthenia, and hysteria), effectively reinventing depression to make room for anhedonia. Anhedonia should be counted the most common of the neurotic disorders, and the most fundamental manifestation of the condition heretofore known as “neurasthenia,” he argued. (The concept of depression as a physical weakness caused by nervous depletion, “neurasthenia,” had been popular among American neurologists since the late nineteenth century. Anhedonia would now replace neurasthenia on the grounds that, like sadness, physical weakness was only one symptom of depression, while for Myerson, apathy was more fundamental.) Furthermore, psychasthenia, which normally included anxiety neuroses, phobias, and obsessive–compulsive conditions, should be reduced by reclassifying the anxiety conditions as variant expressions of anhedonia. This followed from the sense of unfocused nervous energy and oversensitivity to stimuli typically created when anhedonia broke the connection between drives and their normal mechanisms of satisfaction. Although *When Life Loses Its Zest* was widely noticed, Myerson’s concept of anhedonia was not generally taken up by psychiatrists in the decade following its publication, judging by standard texts; “neurasthenia” remained the usual name for mild, neurotic depression, while hysterical, obsessive, and anxiety disorders were still treated as belonging to psychasthenia. In the mid-1930s, few beyond Myerson’s immediate circle appear to have accepted that lack of pleasure and apathy represented a basic mental disorder.37

Given his stance on depression, it comes as no surprise that Myerson should be very interested in a drug that reliably enhanced “pep” or, for him, “energy-feeling.” With little hesitation he tried the new drug on his depressed patients when it became available in 1935, and on himself, too. When, at an American Psychological Association

meeting in September 1936, Myerson already recommended pre-
scribing Benzedrine to “gloomy, anhedonic” depressives as well as
normal people with morning hangovers and low moods, *Time* mag-
azine reported his “favorable results.” Thus Myerson’s enthusiasm
for amphetamine reached the general public as well as the medical
profession. Beyond publicity, Myerson and his Boston circle made
another key contribution to Benzedrine’s success, assimilating the
drug to contemporary biological theory about the chemical mediation
of neural function. At the time it was becoming widely accepted
that signals in the sympathetic nerves were mediated by adrenaline
(or a similar adrenergic hormone—“sympathin,” for Walter Cannon)
released from the nerve endings, and also that the signals of the para-
sympathetic nerves, which generally exerted opposite effects on tar-
get organs, were mediated by acetylcholine. Benzedrine evidently
amplified the effects of adrenergic neurons, either by mimicking the
effects of the chief adrenergic neurohormone or by sensitizing recep-
tive neurons to its effects. Myerson probably supposed that similar
nerve circuits existed in the brain—and, in this thinking, was unlikely
to be alone, at least wherever Cannon’s work was influential. Myerson’s
more original contribution was to suggest that mood disorders were the
result of imbalance between unidentified brain centers tending to sleep
(perhaps cholinergic) and brain centers tending to activity and wake-
fulness (perhaps adrenergic). Amphetamine, the adrenergic agonist,
shifted the balance of brain chemistry in the active, wakeful direction.39

39. A. Myerson, Julius Loman, and William Damashek, “Physiologic Effect of Benzedrine
1936, 192, 560–74; Abraham Myerson, “Human Autonomic Pharmacology XII. Theories
Wilfred Bloomberg, “Effects of Benzedrine in Altering Mental and Emotional Processes,”
Amphetamine (Benzedrine) Sulphate Therapy,” *Am. J. Med. Sci.*, 1940, 190, 729–37; J. D.
University Press, 2001), ch. 3, describes the development of ideas about chemical transmis-
sion in the central nervous system in the 1930s and early 1940s, particularly based on analogy
to peripheral nerve transmission. There was considerable evidence for chemical transmission
as the main mechanism of nerve signaling at the time, but prominent neurophysiologists
fiercely opposed the concept, long delaying its universal acceptance; Elliott Valenstein, *The
War of the Soups and the Sparks: The Discovery of Neurotransmitters and the Dispute Over How
“bible” of the day acknowledged these theories about amphetamine in a backhanded way, by
pronouncing it premature to speculate on the relationship between the drug’s sympathomi-
metic action and its action in the central nervous system; Louis Goodman and Alfred Gilman,
The Pharmaco logical Basis of Therapeutics* (New York: Macmillan, 1941), 437.
Myerson was by no means the only Benzedrine enthusiast among neuropsychiatrists, many of whom were eager to try the new drug on mental conditions. Indeed, members of this specialty accounted for at least a third of an SKF list of over sixty physicians doing clinical investigations onamphetamine sulfate in mid-1936. Some had been commissioned to do studies specified by the firm, but more were freelancers receiving only drugs and placebos from SKF and regularly contacted to see what results were emerging. The first batch of experimental studies with the drug reached publication that year. Myerson, who had begun with the abovementioned investigations of Benzedrine’s effects on the peripheral nervous system in psychiatric inpatients, shifted focus to its central nervous system action and particularly its beneficial impact on the mood and behavior of anhedonics and similar neurotic depressives (mainly outpatients). Eugene Davidoff at Syracuse Psychopathic Hospital tried the drug, along with placebo and ephedrine, on thirty seriously “self-absorbed” patients diagnosed as schizophrenic, finding that about a third of them improved. Almost all patients in this varied population grew more active and talkative on Benzedrine; some became “sultry” or “antagonistic,” but the drug’s stimulatory effects produced improvement for the “asthenic” depressed types, who became more accessible to talking psychotherapy. Alles’s friend Nathanson reported that four-fifths of forty neurasthenic outpatients experienced improvement of their chronic fatigue and exhaustion and an increased sense of well-being, particularly those with low mood. Such elevation of mood, including euphoria, was also found among eighty hospital staff taking the drug as normal controls. Alles’s contacts at London’s Maudsley Hospital, who had begun by investigating the effects of blood pressure on mental conditions, similarly found that depressives benefited from Benzedrine, especially the milder neurasthenic types, but also

40. Wallace memo, 13 March 1936, “Possibilities on Benzedrine Sulfate”; Wallace memo, 16 July 1936, unlabeled folder, box 15, GAP.
some “stuperous” [sic] melancholics.\textsuperscript{44} Around the start of 1937, SKF had decided to pursue the psychiatric market, crafting a circular summarizing this evidence and stating that “the main field for Benzedrine Sulfate will be its use in improving mood,” which the firm sent to a mailing list of 90,000 doctors. Given that the AMA membership had only exceeded 100,000 the previous year, this mailing must have covered the majority of American general practitioners as well as neurologists and psychiatrists.\textsuperscript{45}

**SHAPING THE INDICATION**

An interested group had been identified in the neuropsychiatrists, but the precise way in which amphetamine should be prescribed to “improve mood” was yet to be determined. Nor had other possibilities necessarily been ruled out. During 1937 a second cycle of clinical trials by psychiatrists and neurologists was conducted, many funded by SKF, with the general aim of defining the psychiatric conditions for which Benzedrine is effective. A group at the Mayo Clinic compared a fairly low daily dose of 10–20 mg Benzedrine to placebo treatment, on 100 outpatients carefully divided into three diagnostic groups: anxiety neurosis, chronic exhaustion (neurasthenia), and other (non-neurasthenic) forms of depression. Three quarters of the neurasthenics and other depressives benefited substantially. However, few of the anxious patients improved, most becoming more anxious and irritable instead. The Maudsley group summarized their ongoing studies on hundreds of inpatients, outpatients, and staff taking Benzedrine, and these essentially fit the Mayo findings: the drug benefited many milder depressions but not most severe depressions, anxious states, and schizophrenia. Not infrequently, it made these last two worse.\textsuperscript{46}

The generally rosy reports on amphetamine’s effectiveness for mild, neurotic depressions contrasted with decidedly mixed findings


of studies on more severely ill, institutional patients. For example, another British study with psychiatric inpatients found that about a third of them benefited, mainly the depressives, but certainly not all of them, nor even a predictable type of case. The Syracuse group’s institution-based follow-up study suggested that the drug had more effect on normal controls and alcoholics than on severe neurotics, schizophrenics, and manic-depressives; even in these patients, however, it improved accessibility to talking therapy. A study of schizophrenics in catatonic stupors, conducted at the Palo Alto Veterans Administration hospital, found no benefit from Benzedrine whatsoever. Even Myerson the enthusiast, trying Benzedrine on eighty Boston State inpatients diagnosed with various serious psychoses, found “no improvement in any case,” including a number of severe neurasthenics and manic-depressives in depressed states that one might have expected to improve. To sum up, by 1938 there was substantial clinical evidence that amphetamine was not effective for schizophrenia or for the severe depressions treated mainly in mental institutions, and was only useful as an adjunct to talking therapy, if at all. In contrast, expert opinion held amphetamine to be a promising therapy for milder neurotic depressions, whether caused by adverse events (“reactive”) or by constitutional factors (“endogenous”).

In 1937, SKF applied to the AMA Council for acceptance of Benzedrine Sulfate as a New and Nonofficial Remedy, which would permit advertising along approved lines and also lead to listing in the AMA’s prescribing guide. Approval was granted in December that year for use in narcolepsy and postencephalitic Parkinsonism, and also for mood elevation in depression and other psychiatric conditions. The approval was limited to institutionalized patients, ironically enough, given the emerging clinical evidence. Advertising for these indications soon appeared in the medical journals. This outcome reflected a compromise between the firm’s goal of general approval for fatigue and depression and the AMA’s caution. The Council specifically noted that approval did not extend to use by normal

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people as a “pick-me-up,” and their restriction of Benzedrine’s psychiatric use to institutions probably aimed to forestall the drug’s escape from medical control. Such caution was warranted, since quite apart from prescription of the drug to depressed outpatients, a non-medical “underground” usage of the drug had already emerged. By early 1937, abuse of the drug was reported among midwestern college students (particularly at the University of Minnesota, probably in connection with ongoing trials there), and Benzedrine Sulfate tablets were taking on an identity in the popular imagination as “pep pills” or “pepper-uppers.” There were similar stories of abuse among British students. Students were mostly taking the amphetamine while studying for or actually taking exams. Indeed, some of the earliest psychiatric trials with the drug had reported improvement in test performance, mainly attributed to increased confidence and motivation, a result that was followed up by a number of psychological performance studies (some funded by SKF). Time magazine had covered the student story luridly, condemning the promiscuous use of the “powerful but poisonous brain stimulant.” The Journal of the AMA also commented on it in an editorial, predictably condemning the use of Benzedrine Sulfate without physician supervision, as well as the press coverage. This publicity somewhat worried SKF, which responded by contacting the student health physicians whose reports had made headlines, in an attempt to manage professional impressions of Benzedrine’s safety. The AMA’s subsequent approval suggests that the firm contained this controversy well enough. Not that abuse concerns went away; in 1939, a Purdue University student collapsed

and died during an examination, and the Benzedrine “brain tablets” he had been regularly taking almost certainly played some role.\textsuperscript{51}

Such public relations problems, together with the promise of depression as a market, made the pursuit of certain remaining clinical possibilities for Benzedrine commercially inadvisable. The drug would not be marketed for mental performance enhancement, nor for the control of narcotic addiction, even though some neuropsychiatrists were excited about this possibility. An inherently limited market, narcotic addiction was dangerous ground as well. Sporadic reports of amphetamine addiction were already cropping up in the medical literature. SKF did its best to downplay any association between drug abuse and amphetamine, discouraging freelance clinical researchers that approached the firm to conduct studies on the use of Benzedrine to relieve withdrawal in opiate addicts. (Such studies had sometimes revealed the addictive properties of other new drugs.\textsuperscript{52}) For the time being, neither would SKF market Benzedrine Sulfate for obesity, although the firm followed up early observations by Nathanson and others that Benzedrine resulted in weight loss, for instance sponsoring tests of the drug’s impact on metabolic rate and trials evaluating its effects on appetite. Marketing Benzedrine for weight loss might have interfered with development of the respectable psychiatric market for the drug. Furthermore, the firm might already have realized, amphetamine was selling itself for weight loss, but patent-infringing smaller firms were reaping the profits from most of this use; in this situation, efforts to cultivate the obesity market for amphetamine would not benefit SKF. By the end of the war, SKF would move to capture the weight-loss market, as noted below, but this lies mainly beyond the topic at hand.\textsuperscript{53}


Amphetamine was officially approved as a psychiatric drug, and the initial marketing push focused on depression. In 1939, SKF’s first major campaign advertising Benzedrine for “mild depression” strove both to raise awareness of its prevalence and to promote particular views about the condition. One full-page advertisement from this campaign, which appeared for example in a July 1940 *New England Journal of Medicine*, reads as follows:

The Patient With Mild Depression

The patient with mild depression usually presents a clinical picture characterized by the following symptoms:

1. apathy, discouragement and undue pessimism;
2. subjective difficulty in thinking, in concentrating and in initiating and accomplishing usual tasks;
3. subjective sensations of weakness and exhaustion;
4. hypochondria (undue preoccupation with vague somatic complaints such as palpitation or gastro-intestinal disorders which may have no organic basis)

This advertisement offers diagnostic criteria for depression that cut across camps of psychiatric thinking at the time. “Subjective difficulty in thinking” and accomplishing simple tasks, the second key indicator, was otherwise known as “retardation” and represented a standard symptom of depression in textbooks of the day—although insofar as the sluggishness went beyond neurasthenia, it was usually associated with the major, psychotic depressions. The third key symptom, “subjective sensations of weakness,” represents a straightforward description of traditional neurasthenia. “Hypochondria,” the fourth key indicator, was potentially symptomatic of almost any neurosis, according to standard texts. But most striking about the key symptoms of mild depression presented in this advertisement is that “apathy and discouragement,” equivalent to Myerson’s anhedonia, appears at the top of the list.

This campaign thus redefined and promoted diagnostic criteria for neurotic depression that broadened the condition’s definition in several, not altogether self-consistent ways. It accepted traditional neurasthenia as equivalent to mild depression, while it also made lack of interest and pleasure crucial, along Myersonian lines. Furthermore, it included retardation, traditionally suggestive of major depressive psychoses, and hypochondria, suggestive of neuroses generally (and particularly of anxiety conditions). If taken seriously, this last key symptom would greatly increase the number of diagnosed mild
depressions to include vast numbers of patients in general practice, those whose complaints lacked apparent “organic basis.” The campaign thus worked to expand “mild depression” to encompass a large part of the territory of mental illness, and to make almost anyone within that territory a likely candidate for amphetamine therapy. Advertisements still carried the AMA Council’s requisite warning to hospitalize patients being treated for “depressive psychopathic states.” But naturally, few neuropsychiatrists (or any other physicians) would readily have demanded that paying, neurotic private patients enter a mental hospital as “psychopaths” just to try some Benzedrine tablets. The firm was probably not worried that this precaution would be widely observed.

Smith, Kline and French would not have wanted a strictly institutional niche for the psychiatric use of Benzedrine Sulfate if this outcome could be avoided, and averted it was by 1940. And right from the start, in addition to its marketing to the psychiatric specialty, heavy Benzedrine Sulfate advertising for depression and related psychiatric conditions was targeted at nonspecialists in general medicine journals like the *Annals of Internal Medicine*, *California and Western Medicine*, and the *Journal of the American Medical Association*. For instance, one full-page Benzedrine Sulfate ad run during 1943, entitled “A Milestone in Medical History,” boasted that only a decade earlier “pharmacology had scarcely envisioned a non-narcotic drug capable of alleviating depression,” and forecasted that, through the “revolutionary possibilities it has created in psychosomatic medicine,” amphetamine would rank with insulin in the verdict of medical history. Another run during 1944 was entitled “In Chronic Exhaustion or Depression,” and promised “Immediate Results: Favorable, in some instances spectacular” with depressive disorders of mood, quoting the Mayo study described above. In these nonspecialist journals, SKF also ran extensive campaigns focusing on Benzedrine’s use specifically for the depressed patients most often seen by general practitioners: the elderly, recent mothers, the menopausal, and those

suffering chronic illness. No doubt the firm was capitalizing on the general rise in awareness of neuroses and an increased estimate of their prevalence in the population, often attributed to psychiatry’s prominent role in the American war effort.

Furthermore, though not all advertisements fit this description, SKF’s amphetamine marketing from the mid-1940s tended, perhaps increasingly, to foreground Myersonian thinking, and thus to advance the anhedonia concept of depression. For example, one 1944 advertisement that promoted the use of Benzedrine Sulfate to speed recovery in patients recovering from serious illness or surgery was headlined “when apathy prolongs convalescence,” the reference to apathy invoking Myersonian anhedonia. Another 1944 advertisement promoted its use for “simple depression” by “breaking the stranglehold of pathologically organized habit patterns and by restoring what Myerson calls the ‘energy feeling.’” A third from this same campaign, run in both psychiatric and general medicine journals during 1945, was headlined with a quote from Myerson’s seminal 1922 article, in which he first proposed anhedonia as fundamental to depression. The body of the advertisement quotes more extensively Myerson’s view that talking therapies and physical interventions such as drugs are effective in the same way, while a photo of a beaming white-collar gentleman looking distinctly “better than well” illustrates the results. Only in the 1950s do amphetamine advertisements stress the drug’s use in depression mainly as an aid or adjunct to talking


psychotherapy, the same pattern of accommodation to the ascen-
dance of the Freudians that Jonathan Metzl has described with
minor tranquilizers for that period.58 But in the 1940s, amphetamine
was in itself a therapy for depression, and it became a commercial
success thanks to this marketing strategy stressing the prevalence of
“mild depression” and its treatability by general practitioners as well
as neuropsychiatrists. After all, if (as Myerson thought) “pep and
zeal” are the opposites of anhedonia, and anhedonia is the core phe-
nomenon of depression, then amphetamine—the “pep pill”—is a
specific remedy.

It is impossible to say how many prescribers rationalized amphet-
amine use for depression along these Myersonian lines, and how many
simply used the drug in the same way as the bromides and nerve tonics
still popular among general practitioners in the 1930s and 1940s for a
wide range of neuroses. In any event, amphetamine’s psychiatric use
quickly became widespread. To say exactly how widespread requires
some guesswork, since modern prescription audit data are not avail-
able for the 1940s, but a ballpark estimate is possible. Though amphet-
amine was already used for several purposes, Benzedrine Sulfate
prescriptions can be presumed to roughly reflect amphetamine con-
sumption for psychiatric indications. The basis for this presumption
is twofold. First, at the beginning of 1940 the provisions of the 1938
Food, Drug and Cosmetic Act went into full effect, and amphetamine
tablets were labeled for sale by prescription only. SKF advertised
Benzedrine Sulfate tablets to the medical profession only for psychi-
atric indications until 1947, and mainly for depression. (The drug was
also used by the military during World War II, mostly to counter
fatigue, but these sales were small by comparison.) Second, while amphet-
amine was being widely used for weight control as well, this
expanding market was dominated by smaller drug firms infringing
on the SKF patent and advertising the drug specifically for obesity
(outside mainstream journals), unlike SKF, and charging much less.
It emerged in the courts that just one of these infringing firms—said
to be the world’s largest amphetamine manufacturer after SKF—was
producing on the order of one million amphetamine tablets daily in

108, v; Dexamyl advertisement, “intensive psychotherapy . . . and DEXAMYL to keep depre-
1945, about one-third of which were imitation 10 mg Benzedrine tablets (and the rest, colorful diet pills containing both thyroid and amphetamine). The proportion of this firm’s imitation Benzedrine production that represents psychiatric consumption is probably enough to balance whatever small proportion of SKF’s Benzedrine sales went to weight control, as diet specialists usually prescribed non-SKF amphetamine for this unapproved use. And there were other small, infringing firms making Benzedrine look-alikes too, some of which must also have been prescribed for mental distress. One would therefore be reasonably conservative in estimating that about a million tablets of amphetamine were being consumed daily in America by the end of World War II, by prescription for psychiatric illness, loosely defined—and at least as much again for weight loss.59

Though far short of SSRI anti-depressant consumption today, ongoing use of at least half a million standard daily doses in an adult population not much greater than one hundred million definitely represents a mass-market phenomenon. Benzedrine thus can fairly be called the first “anti-depressant,” a term that appears in promotional material for the drug in the mid-1940s, if by this we mean a drug widely prescribed and consumed to elevate mood for indefinite periods in depressed outpatients. It established the “profile” that subsequent anti-depressants would have to match, the shoes that

59. Benzedrine Sulfate sales for the first quarter of 1943 were $185,000, and were $870,000 for the year; Anon., [1950], “Sales Record of 1-Phenyl-2-aminopropane Sulfate in Tablets,” binder “SKF Accounting to Alles on Products 1936 to Date,” box 11, GAP. 10 mg racemic amphetamine sulfate, the most common Benzedrine dose, twice daily was a typical prescription for depression, and while recommended narcolepsy doses were much higher, there were very few such patients. On production rates, the defendant claimed that Clark & Clark production capacity was only 500,000 tablets per day, while SKF had evidence that the firm had achieved daily production rates of 2,000,000 amphetamine tablets at one point during the war years. The estimate of 1,000,000 tablets daily as Clark & Clark’s production rate is conservative, given this and other evidence introduced in the trial; SKF v. Clark & Clark et al., U.S. District Court N.J., CA 2311, Deposition of William Irby, 22 December 1945, 5, 9–11. On bromides and tonics in the mid-twentieth century, see Callahan and Berrios, Reinventing Depression, ch. 2–4. On the amphetamine diet pill industry in the 1950s and 1960s, see John Swann, “Rainbow Diet Pills in Medical Practice, Industry, and Regulation,” unpublished paper presented at conference on “Drug Trajectories: Historical Studies of Biology, Medicine, and Industry,” Max Planck Institute for History of Science, Berlin, 7–8 June 2002. On the 1938 Act, see Harry Marks, The Progress of Experiment (Cambridge: Cambridge University Press, 1997), ch. 3; see also Temin, Taking Your Medicine; John Swann, “FDA and the Practice of Pharmacy: Prescription Drug Regulation before the Durham-Humphrey Amendment of 1951,” Pharm. Hist., 1994, 36, 55–70; Harry Marks, “Revisiting ‘The Origins of Compulsory Drug Prescriptions,’” Am. J. Public Health, 1995, 85, 109–15. The Inhaler remained available over the counter until the end of the 1940s.
Prozac would ultimately have to fill.\textsuperscript{60} And perhaps it set the stage for future mental health drug marketing in general, by showing how great an impact on sales could result from expansion of psychiatric disease categories.

\textbf{CONCLUSION}

There is not adequate space here to recount amphetamine’s continuing postwar rise and eventual fall as a medicine; suffice it to say that during the 1940s and 1950s the drug was a very commonly prescribed remedy for depression and related neurotic conditions, embraced by general practitioners and psychiatrists alike. In the 1960s, while remaining popular, amphetamine fell from grace for most psychiatric uses, replaced by the minor tranquilizers and the MAOI and tricyclic anti-depressants. But the anhedonia concept of depression did not fall with it. On the contrary, while amphetamine-based anti-depressants were still climbing the sales charts during the first half of the 1950s (such as SKF’s Dexamyl, dextroamphetamine combined with the barbiturate amobarbital so that anxiety would be more strongly reduced), Myerson’s theory that anhedonia or apathy is the fundamental symptom of many depressions finally began to make headway in mainstream medical thinking.

The rise of an idea over time can be hard to measure, but by the early 1950s one finds such signs of anhedonia’s acceptance as the listing, in a 1952 review of mild depressions in the authoritative \textit{Medical Clinics of North America}, of “fatigue, difficulty in concentrating, and lack of interest” as the earliest and most consistent complaints indicating depression. Although “fatigue” harks back to neurasthenia, “lack of interest” resonates strongly with Myerson’s anhedonia, and it fit well with SKF’s ongoing Dexamyl marketing. Nothing corresponding to Myerson’s anhedonia can be found in the American Psychiatric Association’s canonical Diagnostic and Statistical Manual published that same year (widely known as DSM-I) in the definitions of depressions, whether reactive or endogenous. However, at the end of the 1950s, anhedonia appears in Max Hamilton’s highly influential rating scale for depressive disorders severity, under the

\textsuperscript{60} Anon., [1949], “Logical Therapy in the Menopause” Benzebar pamphlet, folder “Piness v. Alles Documents to be Returned,” box 2, GAP. Vos, \textit{Drugs Looking for Diseases}. 
rubric “work and loss of interests.” During the 1960s, a number of anhedonia-measuring assessment tools were developed and used in psychiatric research, indicating the growing estimate of the phenomenon’s importance to the specialty’s understanding of affect disorders. In the 1970s, prominent diagnostic reformulations of depression gave anhedonia a central place, even across diverse schools of thought. Anhedonia stands prominently among the diagnostic criteria for depression in the 1980 edition of the Diagnostic and Statistical Manual (DSM-III), as “loss of interest in all or almost all activities and pastimes,” and “loss of interest or pleasure in usual activities.” Though Myerson himself seems to have been forgotten by the 1960s, Myersonian concepts have become prevalent enough that one Yale neuroscientist could uncontroversially assert, in a recent issue of *Science* magazine, that “one of the key hallmarks of depression is anhedonia.”

It is reasonable to propose, at least as a hypothesis, that the marketing and widespread use of amphetamine as an anti-depressant in the 1940s and 1950s played an important early role in advancing the recognition of anhedonia as a fundamental feature of depression. As the saying goes, given a hammer, one tends to see nails; thus, as a partial explanation, anhedonia may have initially been carried forward on the back of amphetamine, since that drug was the first that psychiatrists could use to intervene directly in depressive symptomatology. Though later anti-depressants were different in profile than amphetamine, the capacity to counter anhedonia remained a standard by which they would all still be judged.


62. For instance, Donald Klein, one of the first research psychiatrists to use tricyclics, came to regard them as acting specifically “on the deranged pleasure center” underlying anhedonia (Klein, “Endogenomorphic Depression,” 452).
Whatever other factors may have played a role in anhedonia’s current importance, I believe I have shown in this study that by 1939, Smith, Kline and French was making this previously little-perceived condition more widely recognized, so that anhedonia would take a place among leading diagnostic criteria for common depressive disorders. The idea that depression was a promising indication for amphetamine may have originated in neuropsychiatry’s positive response to the drug when it was first offered for experimental use in 1936–1937, but SKF soon switched to a more active role to amplify and shape this latent demand identified in the medical profession. The strategy for building prescriptions for Benzedrine Sulfate (and later amphetamine-based anti-depressants) involved shifting perceptions of mental illness. By supporting and publicizing Myerson’s work with Benzedrine, SKF worked to modify medical opinion about the prevalence and nature of commonplace mild depressions. After all, amphetamine successfully alleviates the symptoms of depression when these are understood in terms of impaired “zest for living,” and the drug can readily be perceived to boost what Myerson called “energy feeling.” Furthermore, SKF’s participation in the medical research literature was not limited to “disease mongering,” as it is called today, of Myersonian anhedonia and mild depression in general. The firm won amphetamine’s initial approval through a closely controlled set of researchers sponsored to conduct specified studies on the drug’s safety and efficacy. The firm also managed the search for additional indications through a more complex network of clinical researchers, by funding the sorts of studies the firm sought most, and by discouraging or diverting researchers interested in studies the firm thought would not be to its advantage (for example, studies on Benzedrine in addiction). Once one is aware of all of this concerted, costly effort to shape medical opinion to commercial advantage, it is hard to imagine that it had no effect on perceptions of both drug and disease—then, as now.

What is the historian to make of this drama? For one thing, amphetamine needs to be restored to its place in the history of psychiatry as the drug that paved the way for pharmaceutical treatment of commonplace neuroses. For another, to accommodate the fact that amphetamine was widely accepted as an anti-depressant in the 1940s and 1950s, the historiography stressing a categorical divide between the proponents of talking therapies and those of physical
therapies in American psychiatry requires revision; not only must psychiatry have been more eclectic and complex than this, but the interpretation of psychiatry in the hands of general practitioners, who after all treated the bulk of mental illness and particularly the neuroses, was probably even more eclectic and less polarized. For a third, the rise of the anhedonia concept of depression since World War II invites further historical exploration. And surely, as a general lesson, it is safe to suggest that historians ought to consider the roles of pharmaceutical companies in shaping medical theories and practices during the entire twentieth century, even if the period from the 1910s through the 1940s represents the heyday of scientific medicine. It can be a challenge to uncover such aspects of the history of medicine when both drug firms and their physician collaborators downplay the role of their interactions. Excised from the history of medicine by mutual preference, like the advertising pages habitually removed from medical journals during binding for libraries, little evidence of drug firms’ roles may remain in the literature usually examined by historians. Yet we must remain mindful that absence of evidence for industrial influence on medicine in the past does not constitute evidence of the absence of that influence.