America's First Amphetamine Epidemic 1929–1971

A Quantitative and Qualitative Retrospective With Implications for the Present

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Using historical research that draws on new primary sources, I review the causes and course of the first, mainly iatrogenic amphetamine epidemic in the United States from the 1940s through the 1960s. Retrospective epidemiology indicates that the absolute prevalence of both nonmedical stimulant use and stimulant dependence or abuse have reached nearly the same levels today as at the epidemic's peak around 1969. Further parallels between epidemics past and present, including evidence that consumption of prescribed amphetamines has also reached the same absolute levels today as at the original epidemic's peak, suggest that stricter limits on pharmaceutical stimulants must be considered in any efforts to reduce amphetamine abuse today. (*Am J Public Health.* 2008;98:974–985. doi: 10.2105/AJPH.2007.110593)

THE UNITED STATES IS experiencing an outbreak of amphetamine abuse. The latest national surveys show that about 3 million Americans used amphetamine-type stimulants nonmedically in the past year, 600 000 in the past week, and that 250 000 to 350 000 are addicted.[1] Although survey data indicate that the number of nonmedical users of amphetamine-type stimulants may have stabilized, the number of heavy users with addiction problems doubled between 2002 and 2004.[2] Thus, the public health problem presented by amphetamines may still be increasing in severity; in many ways it surpasses that of heroin.[3] Although all of this is widely appreciated, the history of an even larger amphetamine epidemic 4 decades ago is less well-known.

ORIGINS OF THE EPIDEMIC, 1929–1945

The original amphetamine epidemic was generated by the pharmaceutical industry and medical profession as a byproduct of routine commercial drug development and competition. Searching for a decongestant and bronchodilator to substitute for ephedrine, in 1929, biochemist Gordon Alles discovered the physiological activity of beta-phenylisopropylamine (soon to be known as amphetamine). Alles published his first clinical results with the compound in 1929,[4] began amphetamine's clinical development in collaboration with pharmacologists and clinicians at the University of California, and received a patent on its orally active salts in 1932.[5] Meanwhile, possibly inspired by Alles's work, the Philadelphia firm Smith, Kline and French (SKF) investigated the base form of amphetamine and patented it in 1933. SKF marketed it as the Benzedrine Inhaler, a capped tube containing 325 mg of oily amphetamine base and little else. For congestion, one was meant to inhale amphetamine vapor every hour as needed.[6] Although no legal category of prescription-only drugs existed in the 1930s,[7] the Benzedrine Inhaler was advertised for over-the-counter sale upon its introduction in 1933 and 1934 and for the next 15 years.[8]

At the end of 1934, Alles transferred his patent on amphetamine salts to SKF, and the firm sponsored the drug's further clinical development.[9] In 1937, the American Medical Association (AMA) approved advertising of SKF's "Benzedrine Sulfate" racemic amphetamine tablets for narcolepsy, postencephalitic Parkinsonism, and minor depression.[10] (The voluntary AMA "Seal of Approval" system, in which mainly academic medical experts evaluated data submitted by manufacturers before

allowing advertising in cooperating journals, was the only drug efficacy regulation at the time.[11]) Amphetamine therapy for minor ("neurotic") depression quickly found acceptance among psychiatrists and neurologists in the late 1930s. SKF-funded Harvard psychiatrist Abraham Myerson played a particularly influential role, theorizing that amphetamine adjusted hormonal balance in the central nervous system by creating or amplifying adrenergic stimulation so as to promote activity and extraversion. Because Meyerson understood minor depression as anhedonia caused by suppression of natural drives to action, amphetamine represented an ideal depression therapy to him.[12]

Fueled by advertising and marketing urging general practitioners to prescribe the drug for depression, and at the same time promoting Myerson's rationale for that use, annual sales of Benzedrine tablets (mainly 10 mg) grew steadily to about $500 000 in 1941, over 4% of SKF's total sales.[13] Thus, by World War II, amphetamine in tablet form was finding commercial success and gaining credibility as a prescription psychiatric medication (the first "antidepressant"), despite sporadic reports of misuse.[14] The war years did nothing to diminish the drug's growth in popularity; by 1945, SKF's civilian amphetamine tablet sales had quadrupled to $2 million, including $650 000 in sales of the firm's new "Dexedrine" dextroamphetamine tablets.[15]

The US military also supplied Benzedrine to servicemen during the war, mainly as 5-mg tablets, for routine use in aviation, as a general medical supply, and in emergency kits.[16] The British military also supplied Benzedrine tablets during the war, and the German and Japanese military supplied methamphetamine.[17] Of course, not all amphetamine supplied by the military was ingested by servicemen, nor did users ingest it ad libitum; there were rules limiting the drug's use.[18] However, these were not well observed. For instance, in a 1945 army survey of fighter pilots, of the 15% (13 of 85) who regularly used amphetamine in combat, the majority "made their own rules" and took Benzedrine whenever they "felt like it" rather than as directed.[19]

Along with growth in amphetamine use for psychiatric indications, the war years also saw an explosion of amphetamine consumption for weight loss, although this medical usage was not yet approved by AMA and not advertised by SKF. Off-brand pills manufactured by smaller companies dominated this market. In 1943, SKF filed suit for patent infringement against one of these manufacturers, a New Jersey concern named Clark & Clark, producer of both 10-mg Benzedrine look-alike tablets and colorful diet pills containing metabolism-boosting thyroid hormone and 5 mg of amphetamine. The company's output was a matter of dispute, but on the basis of sworn testimony from both sides, combined amphetamine production for civilian use by SKF and Clark & Clark in late 1945 must have stood between 13 million and 55 million tablets monthly and may be conservatively estimated at about 30 million tablets monthly, each containing 5 to 10 mg of amphetamine salts.[20] This national (civilian) consumption rate for the United States in 1945 was sufficient to supply half a million Americans with 2 tablets daily, the standard dosage schedule for depression and weight loss. Past-year use in 1946 would have almost certainly been higher, because many were only occasional users.

Unsurprisingly, given such widespread availability of so inherently attractive a drug, significant abuse of amphetamine quickly developed. One noteworthy 1947 publication hinted at its dimensions. Psychiatrists Russell Monroe and Hyman Drell, stationed at a military prison in 1945, encountered large numbers of agitated, hallucinating patients. A survey revealed that one quarter of the imprisoned personnel were eating the contents of Benzedrine Inhalers, which then contained 250 mg of amphetamine base. Almost one third of the

Amphetamine was successfully marketed as the first antidepressant in the late 1930s and 1940s, together with a particular understanding of depression as anhedonia.

Source. ***California Western Medicine*** **62 (April 1945): 33 (advertising section) and** ***American Journal of Psychiatry*** **101 (March 1945): xiii (advertising section).**

In the 1950s, competition among pharmaceutical firms boosted amphetamine consumption dramatically, after expiration of the Alles and Smith, Kline and French patent in 1949.

Source. ***Journal of the American Medical Association*** **147 (1951): 19 (advertising section).**

abusers (8% of the prison population) had begun this practice in the military before imprisonment. Only 11% of the inhaler abusers (3% of the prison population) had used some form of amphetamine nonmedically before the war. Twenty-seven percent of abusers had been given amphetamine during military service, mainly by an officer and in tablet form, compared with 5% of nonabusers—an odds ratio of 7.0. There is thus strong evidence that Benzedrine abuse, although an existing practice, was multiplied many times by military exposure, at least among vulnerable subpopulations. And although these prisoners were not typical of military personnel, neither, in the judgment of the psychiatrists, were most of them particularly abnormal young men.[21]

To sum up, by the end of World War II in 1945, less than a decade after amphetamine tablets were introduced to medicine, over half a million civilians were using the drug psychiatrically or for weight loss, and the consumption rate in the United States was greater than 2 tablets per person per year on a total-population (all ages) basis.[22] Up to 16 million young Americans had been exposed to Benzedrine Sulfate during military service, in which the drug was not treated as dangerous nor was its use effectively controlled, helping normalize and disseminate nonmedical amphetamine use. Misuse and abuse, especially of the cheap nonprescription Benzedrine Inhaler but also of tablets, were not uncommon. However, as often occurs in the first flush of enthusiasm for new pharmaceuticals, abuse, adverse effects, and other drawbacks had not yet attracted much notice.

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GROWTH OF THE EPIDEMIC, 1945–1960

In 1945 and 1946, the courts upheld Alles's patent on amphetamine salts, affirming SKF's monopoly control of oral amphetamine until late 1949.[23] With recouped business from infringing firms, SKF's annual sales of amphetamine tablets (Benzedrine and Dexedrine Sulfate) doubled, from $2.9 million in 1946 to $5.7 million in 1947.[24] With AMA approval to advertise amphetamine for weight loss that year, sales climbed further to $7.3 million in 1949, despite competition from methamphetamine-based weight loss and antidepressant products such as Abbot's Desoxyn and Wellcome's Methedrine.[25] Following expiration of Alles's patent in late 1949, consumption of pharmaceutical amphetamines in the United States surged. On the basis of voluntary manufacturer surveys, the Food and Drug Administration (FDA) placed 1952 production of amphetamine and methamphetamine salts at nearly quadruple the agency's 1949 estimate by similar methods.[26] Given that SKF amphetamine sales in the period did not grow significantly, virtually all this expansion in amphetamine supply was driven by the marketing efforts of competitors.[27]

During the 1950s, fierce commercial competition helped drive amphetamine consumption higher still. In a particularly innovative effort to expand medical usages for the drug, in late 1950, SKF introduced a product called Dexamyl, a blend of dextroamphetamine and the barbiturate sedative amobarbital.[28] Intended to overcome the unpleasant agitation that many users experienced with amphetamine and to quell anxiety without drowsiness, Dexamyl was marketed with great success for everyday "mental and emotional distress" in general practice and also as a weight-loss remedy striking at the emotional causes of overeating.[29] Competing firms answered with their own sedative–amphetamine combinations, such as Abbot's Desbutal and Robins's Ambar, blends of methamphetamine and pentobarbital or phenobarbital, respectively.[30] Creative amphetamine combination products from both SKF and its competitors proliferated throughout the 1950s.[31]

According to FDA manufacturer surveys, by 1962, US production reached an estimated 80 000 kg of amphetamine salts, corresponding to consumption of 43 standard 10-mg doses per person per year on a total-population basis.[32] Thus, in amphetamine alone, the United States in the early 1960s was using nearly as much psychotropic medication as the 65 doses per person per year in the present decade that social critics today find so extraordinary.[33] And the 1960s are rightly remembered for excessive minor tranquilizer consumption, around 14 standard doses per person per year on the basis of retail prescription sales.[34] It is rarely appreciated that in the early 1960s, amphetamines were actually consumed at a higher rate than tranquilizers. This oversight may be caused by excessive reliance on retail prescription audits (inappropriate for amphetamines when billions were dispensed directly; see the next section) and neglect of the fact that amphetamine obesity medications were just as psychotropic as amphetamine-based antidepressants. Through the rest of the 1960s, FDA estimates of amphetamine production would grow little beyond 8 billion 10-mg doses, implying that consumption of the drug had already reached saturation levels in 1962. This conclusion, based on voluntary FDA production surveys, draws independent support from flat retail prescription sales from 1964 to 1970.[35]

The best published evidence of the nature and prevalence of medical amphetamine consumption around 1960 comes from studies in the United Kingdom, thanks to the National Health System, which facilitates comprehensive prescription monitoring and correlation of physicians with base populations. A study of retail prescriptions filled in the Newcastle area during 1960 found that about 3% were for amphetamines, consistent both with UK national prescribing figures and with contemporary prescribing in the United States according to commercial audits.[36] Given similarities in culture and medical practices, the British findings therefore shed light on amphetamine use in America around 1960, at least for drugs dispensed at pharmacies.[37]

In the Newcastle study, quantities dispensed were sufficient to supply more than 1% of the total population with 60 tablets per month; two 5-mg doses of dextroamphetamine daily was the most common prescription, according to a 1961 companion study that audited family practitioners in the same area.[38] Dexamyl—in Britain called Drinamyl—was the most commonly prescribed amphetamine product. About one third of amphetamine prescriptions were for weight loss, one third for clear-cut psychiatric disorders (depression, anxiety), and the remaining third for ambiguous, mostly psychiatric and psychosomatic complaints (tiredness, nonspecific pain). The largest age group among the medical users were those aged 36 to 45 years, and 85% of all amphetamine patients were women.[39] Even making the simplifying assumption that weight loss prescriptions were entirely for women and taking into account that women seek medical attention more often than men, these figures indicate that per doctor visit around 1960, a woman was twice as likely as a man to receive an amphetamine prescription to adjust her mental state—much like minor tranquilizers in the same period.[40]

By about 1960, widespread consumption had begun to make amphetamine's negative health consequences more evident. Amphetamine psychosis had already been observed in the 1930s among long-term narcoleptic users of the drug, and individual case reports mounted during the 1940s and early 1950s.[41] Initially, psychotic episodes were attributed to latent schizophrenia "unmasked" by the drug or to some other preexisting psychiatric pathology in the user.[42] In Philip Connell's definitive 1958 study of 40 cases, however, the British psychiatrist persuasively showed that amphetamine psychosis could happen to anyone, and eventually would, given enough of the drug.[43] The highly uniform set of paranoid symptoms—sinister voices emanating from toilet bowls, spies following one's every move—in a wide variety of personality types argued against any shared constitutional feature of the patients' mentality or neurology. Also, the psychosis generally took time to develop, suggesting a dosage-dependent cumulative effect. And although almost all of Connell's patients had engaged in nonmedical use before their crises, a large proportion had first taken amphetamines by prescription, so they could not be dismissed as deviant thrill-seekers. Finally, patients recovered fully a week or two after they ceased amphetamine use, essentially proving they had not been schizophrenic.[44]

Evidence was also emerging around 1960 that amphetamine is truly addictive, instead of merely "habituating" like caffeine, as leading pharmacologists had asserted when the drug was first introduced.[45] Postwar changes in thinking about addiction, promoted particularly by the World Health Organization, facilitated this new perspective on amphetamine by moving the concept away from an

opiate model, defined by acute physiological withdrawal, toward a psychosocial model of "drug dependency" defined by compulsive behavior and erosion of function.[46] Indeed, the previously mentioned British research uncovered evidence of significant dependency on prescribed amphetamines. In Newcastle in 1961, 0.8% of a very large study population received amphetamine prescriptions during a 3-month audit period; according to their physicians, between one fifth and one quarter of these amphetamine patients were "habituated or addicted" or dependent to some extent.[47] Taking the sample in these studies as representative (as the investigators intended), between 2% and 3% of the total population must have received amphetamines by prescription in the course of a year.[48] This, together with the 0.2% of the general population identified as "habituated or addicted," implies a dependency rate among past-year medical amphetamine users of 6.7% to 10%.[49]

To distinguish between the habituation and addiction reported by Newcastle physicians, another northern British study of the early 1960s enrolled family practitioners to dispense Dexamyl tablets, identical-looking placebos, or plain white tablets containing Dexamyl's active ingredients to their apparently amphetamine-dependent patients on a double-blind basis. The study found that about one third of "habituated or addicted" medical Dexamyl users were in fact physically dependent.[50] Taken together with the prevalence estimates in the previous paragraph, this outcome implies extensive iatrogenic amphetamine addiction in the early 1960s—that is, 2.2% to 3.3% of all patients receiving amphetamine prescriptions in a given year.[51]

At the end of the 1950s, the monoamine oxidase inhibitor and tricyclic antidepressants were introduced and quickly acclaimed by psychiatrists as superior to amphetamines for depression. In the United States, however, prescribing rates for amphetamines did not decline significantly in the 1960s,[52] despite the availability of alternatives and increasing awareness of amphetamine's defects. At that time, the vast majority of psychiatric medications were prescribed in primary care, much more so than today.[53] Why, then, did family practitioners continue to prescribe mental health drugs that psychiatric specialists judged inferior?

The answer lies in the type of patient for whom amphetamine-based prescriptions had become typical in the 1950s and the trends and exigencies of primary care. At least one third of primary care office visits are motivated by complaints for which the physician can find no organic explanation, a longstanding fact of life for general practitioners that received official recognition in the 1950s.[54] "Psychosomatic medicine" enjoyed a postwar vogue, and as a substitute for the archaic bromides and nerve tonics then still commonly prescribed, primary care authorities in the 1950s began advocating barbiturates, amphetamine, and amphetamine–barbiturate combinations for the mild depressions and other emotional disturbances presumed to be driving such mysterious complaints.[55] Psychiatric specialists writing on general practice also endorsed these prescribing approaches, although they understood sympathy, reassurance, and time as the main therapeutic agents for all neurotic ailments.[56] Assisted by such trends in medical thought, along with pharmaceutical marketing that reinforced them, amphetamines became first-line treatments for emotional distress and psychosomatic complaints in the 1950s.

In the 1960s, the continuing preference of family doctors for amphetamines caused psychiatrists some consternation. Evidently, the newer drugs did not work as well for the typical distressed amphetamine patient, even though they worked better on bona fide depressives in controlled clinical trials. As one specialist lamented in 1965, general practitioners had tried newer antidepressants, but they prescribed them in subtherapeutic doses to avoid toxicity (in the case of monoamine oxidase inhibitors) and unpleasant side effects (in the case of tricyclics). Used as placebos to tide patients over their difficulties, amphetamines were superior because they were more agreeable and improved compliance. After a brief experiment, many primary care physicians therefore went "back to the old standbys, amphetamine and amphetamine-barbiturate combinations."[57] As one general practitioner explained in 1970, only amphetamine kept certain patients "capable of performing or even enjoying their duties"[58]—that is, of managing their problems of living. In the United States, medical amphetamine use declined only after 1970, when new laws restricted prescribing. In Britain, however, there was a clamor for physicians to show restraint with such dangerous and addictive medicines by the mid-1960s,[59] leading to voluntary moratoriums around 1968 that apparently succeeded in reducing national amphetamine prescribing rates.[60] This difference might be explained by a public health insurance framework in the United Kingdom that reduced

incentives to overprescribe drugs popular with patients.

THE EPIDEMIC'S CRISIS IN THE 1960s

In the early 1960s, amphetamines were still widely accepted as innocuous medications. Apart from vast numbers of middle-aged, middle-class patients receiving low-dose prescriptions from family doctors to help them cope with their daily "duties," in much the same way that their doctors prescribed minor tranquilizers,[61] a significant quasi-medical gray market in amphetamines had developed. For instance, for his painful war injuries and also to help maintain his image of youthful vigor, President John F. Kennedy received regular injections containing around 15 mg of methamphetamine, together with vitamins and hormones, from a German-trained physician named Max Jacobson.[62] Known as a doctor to the stars and nicknamed "Dr Feelgood," Jacobson also treated Cecil B. DeMille, Alan Jay Lerner, Truman Capote, Tennessee Williams, the Rolling Stones, and ironically, Congressman Claude Pepper of Florida, a noted antidrug campaigner.[63] Jacobson's concoctions were peculiar, but he was far from unique in his readiness to prescribe or dispense amphetamines for the price of a consultation.[64]

Large quantities of amphetamines were also dispensed in the 1960s directly by diet doctors and weight loss clinics, many of which were essentially subsidiaries of off-brand diet pill manufacturers. Huge profits could be made when the pharmacist was cut out in this fashion; one dispensing diet doctor paid $71 for 100 000 amphetamine-containing tablets and sold them for $12 000.[65] One widely cited estimate placed the number of amphetamine tablets consumed annually via this channel at 2 billion.[66] Finally, according to the FDA, of the roughly 8 billion to 10 billion 10-mg amphetamine tablets manufactured by drug firms annually in the United States by the late 1960s, up to one half were "diverted" from medical channels altogether.[67] As CBS television revealed in 1964, with a few hundred dollars and a fake company letterhead, anyone could purchase millions of tablets direct from manufacturers by mail, notwithstanding pharmaceutical industry pretensions to self-regulation.[68] When tighter regulation made this tactic more difficult in the later 1960s, wholesale quantities were shipped from manufacturers to Mexico (even to addresses like the Tijuana Golf Course's 11th hole) and immediately reimported.[69]

The FDA's crude population-level amphetamine consumption estimates based on manufacturing surveys (80 000–100 000 kg of amphetamine salts produced for a total population of around 200 million in 1969, or up to 50 10-mg doses per person) were supplemented with prevalence estimates from the first modern drug use surveys. A national survey conducted in late 1970 and early 1971 found past-year usage of amphetamine-type drugs by 5% of American adults. This study was designed exclusively to measure medical, prescribed drug use.[70] A more thorough, roughly simultaneous survey in New York State explored both nonmedical and medical amphetamine use. It found that 6.5% of the state's 13.8 million residents older than 14 years had used amphetamines in the past 6 months. If one counts only those using oral amphetamines made by pharmaceutical firms (the great majority) in the past 6 months, 39% sometimes used them nonmedically and 22% "abused" the drugs, defined as both obtaining drugs without prescription and using them on social occasions.[71]

Because the New York survey's past-6-month medical amphetamine usage rates were lower than, and consistent with, the national survey's past-year prevalence figures, we might reasonably (indeed, with conservative bias) extrapolate the New York study's combined medical and nonmedical usage rates to all 149.4 million Americans older than 14 years. By this extrapolation, at least 9.7 million Americans were past-year users of amphetamines in 1970. If we may also extrapolate the New York misuse rates, 3.8 million took amphetamines nonmedically and 2.1 million abused the drugs by the New York criteria.[72]

To the extent that amphetamine addiction is determined biologically by active compound, dosage form, and dosage schedule or availability, we may safely (again, with conservative bias) apply dependency rates derived from the early-1960s British studies of medical users to the United States of the late 1960s, because the same pills were being distributed on the same prescriptions. If we apply the higher range of the British medical amphetamine dependency rate (reflecting freer supply, predictably higher dependency rates among recreational than medical users, and the more plausible past-year Newcastle prescription rate of 2%) to the inferred national population of past-year medical and nonmedical amphetamine users combined, the United States in 1970 had 970 000 amphetamine users meeting some criteria of dependence and about 320 000 addicts.[73] These should be regarded as minimal figures given the

multiple sources of conservative bias in our national past-year amphetamine usage estimates for 1970 and 1971. Furthermore, 1970 to 1971 prevalence presumably underestimates amphetamine use at the epidemic's peak around 1969, because consumption in the United States was already declining when the surveys were conducted.[74]

As noted, in the United States, large-scale diversion from medical channels was widely acknowledged early in the 1960s, and amphetamine control measures were discussed in Congress throughout the decade. The legislation that in 1965 became the Drug Abuse Control Amendments was originally intended to restrict the manufacture of amphetamines, along with barbiturates. However, the version passed into law stressed penalties for the unauthorized *distribution* of these drugs and the "counterfeiting" of *any* name-brand pharmaceuticals, no matter how safe.[75] The manufacture of such potentially dangerous pharmaceuticals remained "an area where guidance has to be provided without enforcement," as the drug industry's spokesmen urged.[76] National consumption of amphetamines showed no sign of decline following the legislation's implementation.

Drug abuse in general became an increasingly exigent political topic during the later 1960s, as popular concern mounted about widespread amphetamine abuse everywhere from leafy suburbs to Vietnam to hippie enclaves like Haight-Ashbury.[77] In 1969, another congressional hearing was devoted to the theme "Crime in America—Why 8 Billion Amphetamines?"[78] The legislation that emerged, the 1970 Comprehensive Drug Abuse Prevention and Control Act, established the modern set of controlled substance "schedules" in harmony with new international agreements and enabled federal narcotics authorities to establish and enforce production quotas on drugs in the most strictly controlled Schedules I and II. However, reflecting industry interests, only a handful of rarely prescribed injectable methamphetamine products were placed in Schedule II, while some 6000 oral amphetamine products on the US drug market were classed in Schedule III, meaning they were subject to no manufacturing quotas and to looser recordkeeping and their prescriptions could be refilled 5 times.[79] The impact on amphetamine consumption was not dramatic, with reported legal production dropping only 17% between 1969 and 1970.[80]

Although congressional focus on a comparatively small but frightening population of methamphetamine-injecting "speed freaks" spared industry any major inconvenience in 1970,[81] law enforcement authorities had not forgotten that 80% or 90% of amphetamines seized on the street were pills manufactured by US pharmaceutical firms.[82] Civil servants now stepped forward where elected representatives feared to tread. In mid-1971, the Bureau of Narcotics and Dangerous Drugs (BNDD; forerunner to today's Drug Enforcement Administration [DEA]) exercised administrative authority gained under the 1970 act by shifting all amphetamine products to Schedule II, including methylphenidate (Ritalin) and the diet drug phenmetrazine (Preludin), both of which had proved attractive to high-dose injection abusers. Drugs in Schedule II required a fresh prescription each time they were filled, and doctors and pharmacists had to keep strict records or face prosecution. Prescription sales of amphetamines and related drugs shot up when the new restrictions were announced and then plummeted 60% below their original level when they came into effect.[83] Large numbers of doctors and patients obviously realized that their "medical" usage was difficult to justify.

The move to Schedule II empowered federal narcotics authorities, in consultation with the FDA, to set quotas limiting the production of amphetamines to quantities required by medicine. Meanwhile, the FDA was narrowing legitimate uses of the amphetamines, retroactively declaring the drugs to be of unproven efficacy in obesity and depression. Manufacturers were invited to submit applications demonstrating efficacy, but in general these submissions were based on older trials and were found wanting by modern standards of clinical research. Only narcolepsy and "hyperkinetic disorder of childhood" (today's attention deficit disorder, then rare) remained approved usages.[84]

While the FDA pursued its reevaluation of amphetamine efficacy, in 1971, the BNDD took applications from firms wishing to manufacture Schedule II drugs, a procedure that required reporting of past production. According to this reporting, US firms applying for 1971 quotas manufactured 17 000 kg of amphetamine base and 8000 kg of methamphetamine base in 1969. (In terms of the units used in prior voluntary FDA surveys, this figure equals about 3 billion 10-mg amphetamine sulfate tablets and 1 billion 10-mg methamphetamine hydrochloride tablets—altogether, 4 billion doses, a fair estimate of actual medical consumption in 1969 given the context of reporting).[85]

The BNDD originally set 1971 quotas to allow the manufacture of about 15 000 kg of amphetamine and methamphetamine base combined, 40% less than reported 1969 levels. Another 40% cut in the quantity of amphetamines manufactured in the United States was slated for 1972. Given the prescribing slump that followed Schedule II listing, however, the BNDD, with FDA agreement, instead set production levels for 1972 at one fifth of 1971 levels and at one tenth of reported medical production (or about one twentieth of actual production) in 1969.[86] Under the supply controls imposed by the 2 agencies, amphetamines became relatively minor drugs of abuse by the late 1970s, while illicit cocaine use exploded.[87]

Table 1—Estimated Prevalence of Amphetamine Misuse and Dependency in the United States at Peak of First and in Current Epidemics, Expressed as Numbers of Individuals and Percentage of Total Population

Year	Past Year Nonmedical Amphetamine Use, Millions (%)	Physical Dependency or Addiction, Thousands (%)	Total US Population, Millions
1970	3.8[a] (1.9)	320[b] (0.16)	203[c]
2002	3.2[d] (1.1)	303[d] (0.10)	291[c]

Source. For references to footnotes, see endnote 91.
[a]Derived by taking past-6-month New York State usage prevalence figures as indicators of national past-year usage.
[b]Derived by applying upper-range medical dependency and addiction rates from early 1960s in northern Britain to total US medical and nonmedical amphetamine-using population in 1970. Note that the informal but relatively stringent "physical addiction" of the 1960s is not identical to "dependence" as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*.
[c]From the Bureau of the Census.
[d]Data for 2002 are consistent with more recent household drug use survey data.

RECENT TRENDS IN THE LIGHT OF HISTORY

The first amphetamine epidemic was iatrogenic, created by the pharmaceutical industry and (mostly) well-meaning prescribers. The current amphetamine resurgence began through a combination of recreational drug fashion cycles and increased illicit supply since the late 1980s.[88] On the basis of treatment admissions data, methamphetamine abuse doubled in the United States from 1983 to 1988, doubled again between 1988 and 1992, and then quintupled from 1992 to 2002.[89] According to usage surveys, during 2004, some 3 million Americans consumed amphetamine-type stimulants of all kinds nonmedically, twice the number of a decade earlier. As noted, 250 000 to 350 000 of them were addicted.[90] Thus, in terms of absolute numbers, the current epidemic has now reached approximately the same extent and severity as that of the original epidemic at its peak in 1970, when there were roughly 3.8 million past-year nonmedical amphetamine users, about 320 000 of whom were addicted (Table 1). (Of course, the national population then was about 200 million compared with 300 million today, meaning that in relative terms today's epidemic is only two thirds as extensive.)

Another striking similarity between present and past epidemics relates to the role of pharmaceutical amphetamines. Although illicitly manufactured methamphetamine launched the current epidemic, in step with rising amphetamine abuse in recent years, the United States has seen a surge in the legal supply and use of amphetamine-type attention deficit medications, such as Ritalin (methylphenidate) and Adderall (amphetamine). American physicians, much more than those in other countries, apparently are again finding it difficult to resist prescribing stimulants that patients and parents consider necessary, or at least helpful, in their struggle with everyday duties.[91] According to DEA production data, since 1995, medical consumption of these drugs has more than quintupled, and in 2005, for the first time exceeded amphetamine consumption for medical use at the epidemic's original peak: 2.5 billion 10-mg amphetamine base units in 1969 vs 2.6 billion comparable units in 2005.[92] Thus, just as the absolute prevalence of amphetamine abuse and dependency have now reached levels matching the original epidemic's peak, so has the supply of medical amphetamines (Figure 1).

Might the recent increases in both medical and nonmedical amphetamine use be related, and if so, how? Childhood stimulant treatment for attention deficit disorder as a cause of later nonmedical amphetamine consumption is one possible connection that has received considerable attention. Although controversy remains, the weight of evidence suggests that medication prescribed for attention deficit disorder does not predispose individuals to stimulant abuse or dependence.[93] Moreover, if there is a statistical association, it may link stimulant misuse to attention deficit disorder per se (rather than to medication),[94] as one would expect if some nonmedical amphetamine use is in fact self-medication. Nevertheless, this line of inquiry does not eliminate any possible relationship between prescribing for attention deficit disorder and rates of stimulant abuse. Even if there is no connection at the

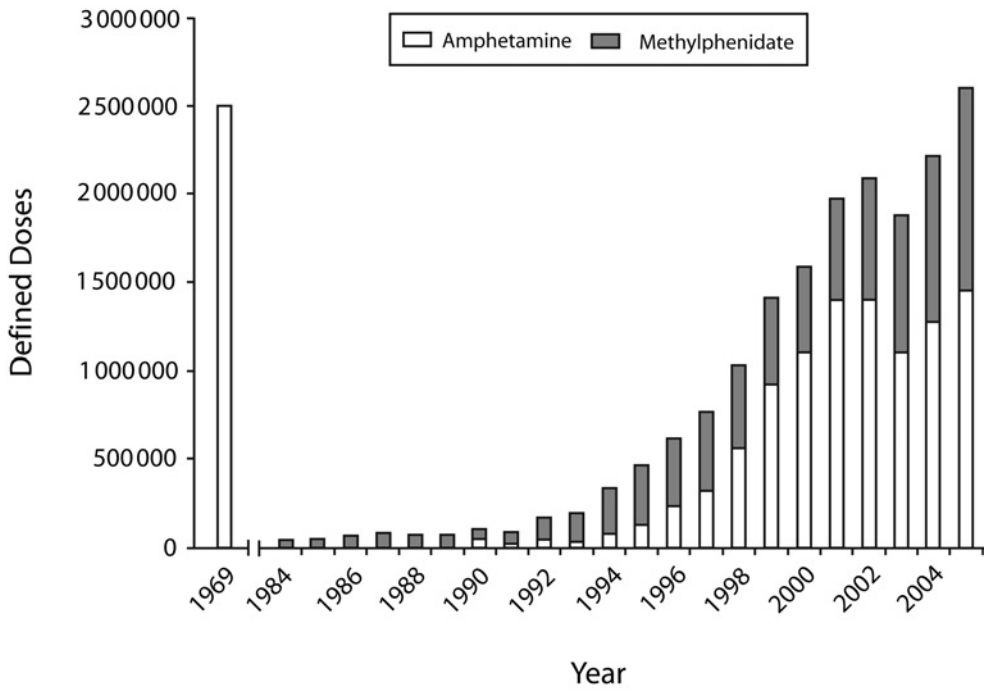

FIGURE 1—US medical consumption of amphetamine and methylphenidate, expressed as common dosage units (10-mg amphetamine and 30-mg methylphenidate, anhydrous base), based on Drug Enforcement Administration production quota figures.[92]

individual level, there may be one at the population level.

Other than converting attention deficit disorder patients into abusers, prescribed amphetamines can contribute to the national stimulant epidemic in at least 2 other ways. For one, the mere distribution of so many stimulant tablets in the population creates a hazard. Diversion from students with attention deficit prescriptions to those without is known to occur in high schools, and at American universities, both diversion and nonmedical use by those with prescriptions are commonplace.[95] In 2005, some 600 000 Americans used psychiatric stimulants other than methamphetamine nonmedically in the past month.[96] Thus, legally manufactured attention deficit medications like Adderall and Ritalin appear to be supplying frequent, and not just casual, misusers. A detailed analysis of stimulant abuse in recent national household drug surveys found not only that 1.6 million of the 3.2 million past-year nonmedical users of stimulants in the United States used strictly nonmethamphetamine psychiatric stimulants in the past year, but that over 750 000 of them had never used any stimulants except attention deficit pharmaceuticals *in their entire lives*. In that study, those who abused only nonmethamphetamine (i.e., pharmaceutical) stimulants in the past year accounted for one third of the approximately 300 000 Americans estimated to be amphetamine addicted (reflecting the fact that nonmethamphetamine users have a somewhat lower rate of frank addiction than methamphetamine users.[97] On this evidence alone, one can fairly describe the high production and prescription rates of these medications as a public health menace of great significance.

Besides iatrogenic dependence and diversion to nonmedical users, there is another way that widespread prescription of amphetamine-type stimulants can contribute to an amphetamine epidemic. When a drug is treated not only as a legal medicine but as a virtually harmless one, it is difficult to make a convincing case that the same drug is terribly harmful if used nonmedically. This is what happened in the 1960s and is presumably happening today. Thus, to end their rampant abuse, amphetamines had to be made strictly controlled substances and their prescription sharply curtailed. Today, amphetamines are widely accepted as safe even for small children, and this return of medical normalization inevitably undermines public health efforts to limit amphetamine abuse. We have not yet reached the point where up to 90% of the amphetamines sold on the street are products of US pharmaceutical firms, as the federal narcotics chief reluctantly admitted before Congress in 1970.[98] But with half the nation's nonmedical users evidently consuming pharmaceutical amphetamines only, the comments made by Senator Thomas Dodd in those hearings echo strongly today. America's drug problems were no accidental development, Dodd observed; the pharmaceutical industry's "multihundred million dollar advertising budgets, frequently the most costly ingredient in the price of a pill, have pill by pill, led, coaxed and seduced post–World War II generations into the 'freaked out' drug culture" plaguing the nation.[99] Any effort to deal harshly with methamphetamine users today in the name of epidemic control, without touching medical stimulant production and prescription, is as impossible practically as in 1970—and given historical experience, even more hypocritical. ■

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