

Social Context and Health Consequences of the Antipsychotics Introduction

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Background. From the vantage point of fifty years after the introduction of antipsychotics to clinical practice, this article examines the social context and health consequences of their introduction.

Methods. Historical review of literature sources with commentary.

Conclusions. The availability of antipsychotics over nearly half a century has powerfully influenced concepts of mental illness, dominant models of care versus control, health outcomes and side effect burdens. The large demand and economic success of antipsychotic medications is an important driver for research and development as well as sophistication in marketing. Regulatory agencies, funders and clinicians are faced with a moving target as indications for use of antipsychotics move well beyond the traditional core of schizophrenia and acute mania into depression, anxiety, behavioral disturbance with dementia and some forms of personality disturbance. The history of antipsychotics and mental illness is arguably being written as forcefully now, in an environment of rapid scientific change, as was the case in the 1960s era of rapid social change when chlorpromazine prompted a shift of emphasis from asylum to community. Psychosis is a challenge to how we interpret and approach our inner experiences and societal structures. Accordingly, it is not surprising that the history of antipsychotic drugs resonates with a lively interplay of social, health and economic issues and an ongoing quest to comprehend mental phenomena and their variants.

Keywords Antipsychotics, Social, Health, History, Deinstitutionalization, Health outcomes

INTRODUCTION

Antipsychotic medications have been used in clinical practice for over fifty years. They were introduced at a time when therapeutic interventionism had gained sway over the inertia built up during a century of institutional care. Electroconvulsive therapy, insulin coma and prefrontal leucotomy all came into use between the mid 1930s and 1950s. In the same period barbiturates, opiates and paraldehyde were well-established sedatives in the pharmacopoeia and were used to quell psychotic agitation (1). However these diverse treatments were variously supplanted or marginalized by the advent of the antipsychotics. The first of these was chlorpromazine, synthesized in 1950, and first reported in the treatment of mental illness by Delay in 1952 (2). Chlorpromazine was both tranquillizing, that is quieting without marked somnolence, and

associated with reductions in some core symptoms of psychosis, namely hallucinations, delusions, thought disorder and associated behavioral disturbance. Although an antipsychotic action had been noted two decades before with rauwolfia (3), chlorpromazine was the first synthetic drug to evince such a clinical effect and was rapidly adopted by clinicians. The antipsychotic effects of reserpine, derived from rauwolfia, were confirmed in 1954 by Kline (4) and later the same year by Delay and others (5).

THE SCIENTIFIC FERMENT

It was not a new idea to seek relief of mental suffering using chemical means. Rauwolfia had been used in Indian ayurvedic medicine for centuries. Many psychoactive substances were recognized and some already widely employed in clinical practice, notably barbiturates and amphetamines. However, chlorpromazine was developed at a time of particularly rapid growth in scientific understanding both in pharmacology and of brain function. The rise of industrial chemistry, particularly

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through the dye industry, had advanced the synthesis of compounds and in turn spurred research into their effects in humans. The success, both commercial and in relief of symptoms and disease, of drugs such as aspirin for headache (6) and Salvarsan arsenicals for tertiary syphilis (7), suggested that other neurological and psychiatric presentations could be ameliorated by appropriate compounds. Against this “can do” background, chlorpromazine was synthesized as a variant of antihistamine compounds by Charpentier in 1950, reported as a potential adjunct to anaesthesia for surgery by Laborit (8), and its effects in psychosis reported by Delay, all in the space of two years (see chronology in Deniker, 1989). This is a breathtaking pace compared to the present day drug development process. The available methodological advances in pharmacology research, including animal testing and the controlled clinical trial, added further impetus to the clinical uptake of the drug. The first international symposium on the subject of “Chlorpromazine and Neuroleptic Medication in Psychiatry” was held in Paris in 1955. At that meeting the results of three double blind trials were presented by the British psychiatrist researcher Linford Rees. These were on the treatment of anxiety states, anxiety in asthma, and effects on autonomic functions as a prognostic indicator (9). Such methodology added weight to the animal data plus clinical observational approach of Delay and colleagues (2) whose seminal paper reported the outcome in 20 patients receiving regular intramuscular or oral doses of the drug. Delay targeted cases with *neuro-végétatif* substrates such as excitation, depression, confusion, insomnia and anxiety; of his cases only six had mania and two schizophrenia. This broad sweep of enquiries illustrates an open mindedness to clinical uses for the drug, as well as the deployment of cutting edge methodologies in psychiatric research. Interest was international, including publications by French, Swiss, British, American and Canadian authors, on chlorpromazine and reserpine, by 1954. It is of note that in early use chlorpromazine was not specifically anticipated as a selectively anti-schizophrenia or antipsychotic drug. Indeed Delay (2) frowned on the suggestion that the drug produced a *lobotomie chimique*, citing the absence of the euphoria, hyperactivity, confusion or sphincter disturbance sometimes seen after leucotomy.

A clear understanding of mechanisms of action was not available at the outset but developed rapidly. Dopamine had been identified but its function in the brain was not understood. Carlsson elucidated the importance of dopamine in the reserpine syndrome in 1958 and in 1963 reported the action of chlorpromazine and haloperidol as dopamine depleting agents (10). This level of precise knowledge of brain function, drug action and clinical effects, incomplete though it may be, has been of profound importance. It has fostered the development of biological psychiatry, the prestige of drug treatments in psychiatry, and the willingness of funders to support their widespread use. The scientific aura of antipsychotics received further support from the roughly parallel introduction of antidepressants (11), with analogous discoveries of their effects on other monamines (12). A further consequence of understanding a

specific mechanism of action was the development of the dopamine hypothesis as an explanation of the aetiology of schizophrenia, and the reification of schizophrenia as a distinct biological disease process requiring specific treatment with antipsychotics.

The notion of biological causation of mental illness, enshrined a century earlier in Griesinger's dictum *Geisteskrankheiten sind Gehirnkrankheiten* (mental illnesses are brain diseases) (13) was given substance by these discoveries. It contributed to a slow and ongoing reorientation by society to the proper understanding, care and control of the severely mentally ill. This had been previously typified by prolonged involuntary admission to asylums with attendant separation from society and stigmatization. For the lay public, the aetiological and pathophysiological concepts of the dopamine hypothesis and of the monamine hypothesis of depression have entered the vernacular in the metaphor of a “chemical imbalance” in the brain causing mental illness.

Thus the combination of products of industry, insights into brain function, and the increasingly structured observations of clinicians, assisted the birth of specific chemical treatment of psychosis. This was an iterative process and the acceptance of chlorpromazine and later antipsychotics gave extra warrant in turn to the value of the scientific enterprise. They also reinforced a faith in further drug development that remains strong today and is a leitmotif of the pharmaceutical research and development effort, viz. the continuing search for a “magic bullet.” This was the term coined by Paul Ehrlich that guided his painstaking research on arsenical treatment for syphilis in the first decade of the 20th century. A magic bullet is an “ideal” compound that targets a specific disease without harming the host. That is, efficacy without side effects. Whilst antipsychotic medications fall well short of this benchmark, the various patent, licensing, practice guideline and funding mechanisms for medications promote the ongoing search for magic bullet qualities. This regulatory environment rewards innovation, places a premium on improved efficacy and reduced side effects, and seeks cost benefits, particularly after a patent expires. This has spurred the development of a generation of atypical antipsychotics as well as basic research into schizophrenia, including in recent years laboratory genetics and molecular biology. This innovation-oriented culture, now widespread around the world, has received significant impetus from the economic dynamism and research productivity of the pharmaceutical industry, where CNS products account for around a third of the market and are prioritized in pipeline research.

THE FERMENT OF SOCIAL CHANGE

From the 1850s onwards many economically developed countries around the world voted large sums of money and resources to the building of asylums. These provided comprehensively for the basic needs of patients committed to them: full board and lodgings, nursing and medical supervision,

religious instruction, spacious grounds. Many had attached farms and provided work roles for patients within the institution as an aid to self-sufficiency. This sheltered existence came at a price. Admission was usually involuntary and length of stay, at the discretion of the superintendent or his nominee, could be indefinite. Internal malaise in the increasingly large closed institutions was often to the detriment of patients and special inquiries and calls of concern by governments and advocacy groups were common.

One impulse for founding asylums initially was to make appropriate provision for the deserving mentally ill who had previously been mixed in with petty criminals and the destitute in workhouses and poor houses. This form of social warehousing had been a marked historical development. In the UK the introduction of the new poor law of 1834 attempted to restrict support to those living "within the House," as these institutions were termed, and introduced the principle of "less eligibility" whereby workhouse conditions should be less than of the lowest paid laborer outside. Society was experimenting with a large-scale authoritarian administrative approach to social ills. Seen against the ethos of work and poorhouses, the provision of separate asylums was a step up for the mentally ill, whilst at the same time assisting in regulating the social order in an increasingly complex industrial society.

The largesse of and centralized planning by Government with respect to the mentally ill in the initial phase of institution building is well illustrated by developments in Victoria, Australia in the 1850s (14). Much of the world was in the grip of European colonial expansion. The associated exploitation of natural resources poured significant wealth into government coffers. Melbourne was briefly the world's richest city thanks to the gold rushes between 1850 and 1858. When the "diggers" (miners) moved on, social problems remained including an increased number of people with severe mental illness, partly attributed at the time to gold fever. Following rivalry between competing local councils and careful attention to finding healthily situated locations, two asylums were built, in Ararat and Beechworth. These were two of the largest gold field centers that had contributed much to the Treasury but were in sharp decline after the gold ran out. Grand edifices were duly erected in these remote centers and opened in 1867, remaining in use until a decade ago in what continued on as small rural centers. At that time, wealthy societies did not aim to stint on public works for the proper provision of care of the mentally ill, an impulse at once benevolent, pragmatic and exclusionary.

With improved standards of living in the broader community over the next century much of the Dickensian background resolved and the original motivations to create asylums lay in a distant past. The beginnings of modern welfare states in the 1940s further improved the lot of the general populace, yet patients remained separated from the community in an institutional time warp. That other great bastion of institutional care, the tuberculous sanatorium, was closing in response to new treatments with antibiotics. The antipsychotics thus arrived at a propitious time. They provided a model of treatment that was

transferable beyond the walls of the asylum — the treatment could be self administered by the individual at home — and also bore the stamp of scientific respectability. Increasingly institutionalization within asylums was recognized as a malign factor. Social and occupational therapies with rehabilitation to the community, combined with ongoing antipsychotic medication, displaced custodial care as the primary dynamic of the now diminishing asylum settings.

Shepherd (15) has noted that asylums were changing before the availability of the antipsychotic drugs, with the introduction of social and occupational programs, and a less restrictive ethos (16). These changes were associated with trends to discharge that were continued but not conspicuously increased by the advent of medications such as phenothiazines. Ødegaard in 1964 reported that in hospitals with favorable therapeutic situations psychotropic drugs, both antipsychotics and antidepressants, had little observed effect on discharge rates but that in hospitals with a low pre-drug discharge rate the improvement was considerable (17). Thus both psychosocial and antipsychotic treatments have a reasonable claim to playing important and indeed complimentary roles in the shift away from custodial care. Community care became the new ethos and developed into a movement around the world (18).

The increased emphasis on community care has wrought further social changes including the need to educate the public regarding mental illness, most recently through internet sites. Community based initiatives include support groups for families such as the National Alliance for the Mentally Ill in the U.S., development of supported accommodation and life skills programs such as run by Richmond Fellowship in many countries, and peer support networks for consumers such as "schizophrenics anonymous" run by the National Schizophrenia Foundation in the U.S. These and many other reputable organizations provide up to date information about antipsychotic medication and other treatments as well as discussion forums where consumers and carers can discuss pros and cons. By contrast to the asylum era the emphasis is on respect for the autonomy of the individual, support for living in the community and accessing evidence based treatments, advocacy for appropriate levels of health resources to address the recognized level of disease burden and for research to further understanding of causes and solutions. Far from being secreted behind the walls of the asylum, people experience psychosis under the gaze of the general public and this in turn requires careful attention to public attitudes to mental illness as well as engaging with the at times harsh glare of the media.

Whilst a number of these changes are gratifying, sharp criticisms of current social outcomes in psychosis are also justified. Homelessness is a significant issue and may commence in the early stages of a psychotic illness (19). Imprisonment is another adverse outcome (20). It is difficult to see either as superior to asylum care. Both permissiveness and authoritarianism have downsides and the health and justice systems have attempted to devise new systems to bridge the gap. These include assertive outreach community services, community

treatment orders and more careful attention to assessment and management of risk.

HEALTH BENEFITS OF ANTIPSYCHOTICS

The World Health Organisation's Global Burden of Disease study in 1996, applying a common metric to assess disability across all disease categories (Disability-Adjusted Life Years or DALYs), reported four of the top ten single diseases causing disability to be psychiatric disorders, plus alcohol abuse a fifth (21). Schizophrenia accounted for 2.6% and bipolar disorder 3% of total disease burden, due to the combination of impairment and chronicity of these diseases in many patients. This and related studies have raised the profile of psychoses at a population health level and emphasized their importance in health planning.

The burden of disease figures are contemporary, they reflect disability associated with schizophrenia in populations where antipsychotic medications have been available for most of the lifetimes of those affected. On the other hand a substantial corpus of antipsychotic efficacy studies clearly demonstrate symptomatic improvements, decreased socially disruptive behavior, reduced relapse rates, and improvements in domains of neurocognitive deficits, negative symptoms and quality of life measures. The more comprehensive studies have been amassed for drugs still under patent where the costs of the research can be justified as an investment to obtain a clinical indication as well as the sales potential of additional data. However most such studies include comparator drugs, particularly haloperidol, that in effect provide an historical control.

The apparent conundrum of high burden persisting in the face of available effective antipsychotic treatments is not clearly resolvable using historical perspectives. The historical data is limited and comparisons can only be loosely drawn. Much of the disability and burden of illness associated with severe psychosis prior to the 1960s was contained in and masked by institutional settings. The social changes and scientific advances outlined above are rich and substantial; by contrast the diseases of schizophrenia and bipolar disorder remain relatively resistant to interventions, be they biological, psychological or social, developed so far. Adherence rates are poor even where effective treatments are available, especially for antipsychotics in chronic psychosis (22). On a sobering note, Andrews has recently costed averting one year lived with disability due to schizophrenia at AUS 200,000 dollars (around US\$145,000), calculated from an average 13% improvement in disability with current treatment, and a potential 22% improvement for the same cost with optimal delivery of available evidence-based treatments (23). Interestingly, these figures highlight the ongoing importance of the curiosity, careful clinical observation, and scientific approach adopted over 50 years ago by Delay, Deniker, Kline and others. There is much more to be learnt about these conditions and a substantial

research effort worldwide is responding to this challenge using exploratory methods barely conceived of 50 years ago.

The antipsychotic medications have reduced positive and some deficit symptoms of illness for many individuals, facilitated a sweeping social change of the locus of care and control towards the community and towards autonomy, and countered some superstitious and stigmatizing beliefs about the illness with a simplistic but accessible biological explanation. The resolution of the conundrum is that efficacy studies are focused on change from baseline, burden studies on how far the baseline, even after treatment, lies outside population norms. Efficacy has a triumphant voice, burden a more sobering tone. Further, the pharmacological explanatory and treatment model is a lever for changes in social attitudes and health service deployment, over and above changes in any individual treated.

The application of antipsychotic medications to schizophrenia and bipolar disorders are evolving fields with recent increased interest in treatment effects on associated depression and anxiety symptoms (24). Research has also been conducted on unipolar depression and anxiety disorders in patients without a history of psychosis (25) and on the use of low dose antipsychotic medication to avert emerging first episode psychosis (26). This wider range of enquiry is reminiscent of the broad spectrum of clinical applications explored by the pioneers of chlorpromazine treatment in the early 1950s, except that economic considerations, that is sales potential, is now a more powerful dynamic. A high return is necessary to support investment in the more rigorous and hence more expensive methodological frameworks required to establish marketing indications and convince funders or consumers themselves of cost-benefit.

HEALTH BURDENS OF ANTIPSYCHOTICS

The history of antipsychotic use, extending across a multiplicity of compounds and a half-century of clinical practice, delivers interesting insights into how a full appreciation of side effects continues to evolve and is managed in patient care. Delay's 1952 paper particularly noted postural hypotension, somnolence and some indifference. Steck in 1954 described the "syndrome extra-pyramidal et d'encéphalique" seen in treatment with both chlorpromazine and reserpine, noting both parkinsonian and hyperkinetic features. This report of the striking similarities between these two drugs is reported by Deniker (1989) to have been the inspiration for the development of he and his French colleagues concept of neuroleptics in 1957, the definition of which includes producing both antipsychotic action and extrapyramidal side effects.

Some drugs had particular side effects or were particularly noted for them such as agranulocytosis and recently cardiac effects (27) with clozapine, QT interval prolongation with thioridazine, cholestatic jaundice with chlorpromazine. Specific syndromes became recognized such as neuroleptic malignant syndrome and tardive dyskinesia. As chronicled by Tarsy (28)

the latter term was coined in 1964 after a decade of antipsychotic use, though the first case reports of dyskinesias, persisting after discontinuation of short-term treatment with chlorpromazine, were reported in 1957. The syndrome was held to be rare until more systematic surveys were undertaken in the mid to late 1960s. Overall the side effect profile and particularly tardive dyskinesia tempered enthusiasm for neuroleptic use and contributed to a narrowing of the clinical uses of these drugs to treatment of psychosis, in particular schizophrenia, where there was no obvious alternative drug class to choose from. This trend has reversed somewhat with the advent of the “atypical antipsychotics” most of which produce less extrapyramidal side effects than the more classical or “typical” drugs, though some are associated with weight gain and associated concerns about diabetes and cardiovascular risks. However the lesson from the past 50 years is that the appraisal of side effect burdens, particularly given the possibility of long-term emergent neurological syndromes such as tardive dyskinesia, requires judicious appraisal over a lengthy period.

Clinical practice has adapted to this changing profile of side effects, for example with haematological monitoring programs for clozapine, and with exercise programs to minimize weight gain. A related concern that has yet to be successfully addressed is the high rate of smoking in patients with psychosis, the consumption increasing with dose of typical antipsychotic (29). This latter, with its attendant physical health risks, is an interesting example of changing times with cigarettes having been an element of token economies in some asylum settings and dispensed to patients as rewards.

As well as the more technical and factually oriented interest in side effects, the antipsychotics have engendered their share of criticism in terms of divergent world-views on mental illness and concerns regarding potential abusive uses. The drugs are sometimes used in nonconsenting involuntary patients. They have at times been vehicles for political abuse in enforced treatment of dissidents. The medical model of psychotic disease remains inconclusive in terms of fundamental mechanisms, and social and existential theories of the development of psychosis have at times had many adherents. In the 1960s there were widely discussed aetiological theories based on double binds and the “schizophrenogenic mother” (30). In the anti-psychiatry movement Laing considered people with schizophrenia to be reacting to an insane world (31); a world then in the grips of nuclear threats during the cold war standoff. Drugs were seen as misapplied when used to treat ills conceived in this way. Drugs were also seen as an extension of social control by an authoritarian state seeking to control behavior it did not approve of (32,33) or, similarly, as a profit making exercise by “big pharma” (34) drawing on the increasing medicalization of emotional and social problems (35). Within the profession of psychiatry, commentators noted the often-polarized polemic between proponents of psychodynamic and biological viewpoints (36).

Psychosis is evocative and challenging. By extension, so is any treatment method for psychosis and the values that underpin it, as well as how society responds to its availability. The same debates are not to be found for treatment of diabetes with insulin or gout with allopurinol. Such debates and their many variants illustrate the complex threads in the history of psychosis, its interpretation, and how it is approached by others and through societal structures.

CONCLUSIONS

There have been substantial changes in psychiatry over the past half-century since antipsychotic medications were introduced into clinical practice. The complexity of factors contributing to societal and health service changes preclude simple attributions of cause and effect.

Most striking is the dominant position that antipsychotic medications have maintained over this period as the drug treatment of choice for schizophrenia, and more broadly for symptoms of psychosis — delusions, hallucinations and thought disorder — in other conditions such as mania or psychotic depression. Chlorpromazine rapidly displaced treatments in favor for schizophrenia before its introduction and, though the pharmacological profiles of antipsychotics have continued to evolve, the core of post-synaptic dopamine receptor antagonism remains.

There are three particularly cogent and mutually compatible ways to explain this success — the professional, commercial and societal. Firstly, the discovery of this class of drugs fortuitously opened a window on brain function in relation to psychosis and introduced pharmacopoeia-standard treatments for these conditions for the first time. The effects on psychosis were so striking that case studies were sufficient to convince clinicians of their utility and to spur further confirmatory research using more formal methodologies. Secondly, these were synthetic compounds enjoying patent protection and there were profits to be made by promoting their use and furthering research into future refinements. Thirdly, society grasped firmly the notion of a specific chemical remedy for the age-old concern of psychosis, with its implicit biological explanation of the emanations of these illnesses. This opened the way for the gradual dissolution of an expensive and socially outdated asylum system and the repositioning of psychosis as a more conventional illness susceptible to ongoing control through daily treatment. Rather than rejecting what was irrational by excluding the insane in asylums, it was now more practicable to interpret insanity using a rational disease model and allow those affected to resume a place in the community. That this has been only a qualified success in terms of health outcomes is emphasized by the contemporary figures on burden of disease and in continuing concerns about rates of homelessness and imprisonment in individuals with chronic psychosis. This dynamic of advances in treatment yet persisting neglect of the chronically mentally ill by society was

noted by Tournay over 30 years ago (37). This emphasizes the importance of continuing to strive to influence public attitudes and social policy as well as targeting symptoms and function of affected individuals.

A more recent trend is for antipsychotics to be reappraised and potentially repositioned as treatments for symptoms in a variety of presentations including anxiety and depression, whether comorbid with psychosis or occurring in their own right, rather than as "anti-schizophrenic" or antipsychotic agents per se. From the perspective of a long historical cycle of half a century, and given the present vigor of research into genetics and neuroscience, it appears that the "antipsychotics" may be entering a further dynamic phase in their historical development and that society, professionals, industry and health services will both shape and respond to such developments as has been the case since their inception.

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