A Guide to the Extrapyramidal Side-effects of Antipsychotic Drugs

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1

The background

Introduction

It is always comforting to reflect on a 'Golden Age' – a time of optimism and hope when the barriers of ignorance and impotence tumbled before an onslaught of knowledge.

For psychiatry, the decade of the 1950s might now be seen as one such Golden Age, for the 1950s saw the explosive birth of psychopharmacology. Suddenly, those devoted to the medical management of individuals suffering the ravages of psychiatric disorder had at their disposal an ever-expanding array of therapeutic tools whose efficacy could be established by the application of scientific principle, which did not require a lifetime to show their benefits, and which were relatively cheap. No longer was the therapeutic armamentarium restricted to those who were sufficiently intelligent and articulate to utilise what was on offer, or sufficiently well-heeled to afford it. For no longer would psychiatrists need to be pseudo-physicians, misdirecting their medical skills to crude and largely ineffective physical interventions or suffocating them under a welter of unverifiable dogma. Most importantly of all, no longer were those whose misfortune it was to be afflicted by major disorders excluded from the therapeutic possibilities.

It was, of course, necessary to interpret the concept of knowledge in this 'Golden Age' in a somewhat wider than usual manner, for while it may have been clear that the increasing litany of new compounds worked, understanding of *how* they worked was rudimentary. This nonetheless had a bearing on the other exciting prospect on offer – the availability of a series of tools to explore the functionings of the human brain.

Table 1.1. *A chronology of 1950s' psychopharmacology*

	1949	Cade	The antimanic (and maintenance) effects of lithium salts
December	1950	Charpentier	Synthesis of chlorpromazine
December	1951	Sigwald & Bouttier	First treatment with chlorpromazine
March	1952	Hamon et al.	First publication of the efficacy of chlorpromazine
May	1952	Delay & Deniker	First systematic evaluation of chlorpromazine
	1952	Selikoff	Mood-elevating effects of isoniazid
	1954	Steck Thiebaux	First formal accounts of parkinsonism with chlorpromazine
	1954	Kline	Reserpine
	1954		Methylphenidate
	1955		Meprobamate
	1955		First trial of G22355 (Imipramine)
	1955	Delay	'Neuroleptics'
	1956	Ayd	Identification of dystonia with chlorpromazine
	1957	Kline	Introduction of MAOIs
	1957	Kuhn	First report of antidepressant effect of imipramine
	1957	Randall	Behavioural effects of 1,4 Benzodiazepines
	1958	Petersen	Thioxanthenes
	1958	Janssen	Butyrophenones (haloperidol)
	1958	Zeller	MAO inhibition
	1959		Introduction of imipramine
	1959	Sigwald et al.	First report of tardive dyskinesia
	1959		Clozapine
	1960	Cohen Tobin	Anxiolytic effects of chlordiazepoxide

The Golden Age

The onslaught of compounds introduced into clinical practice was relentless (Table 1.1). Chronologically, it actually began in 1949 when the Australian psychiatrist John Cade reported the antimanic and mood-stabilising properties of lithium salts. It has to be

admitted that the theory behind the work which led to these observations was frankly awry, but the consequence was to be enormous when, in other places, the therapeutic potential was brought to clinical fruition.

The rauwolfia alkaloid reserpine, long associated with Ayurvedic medicine, was introduced into Western psychiatry by Nathan Kline in 1954, the same year that the central stimulant methylphenidate became available, though this would have to endure the controversies of several decades before it would find respectability – of sorts.

In the early years of the decade, the inappropriate elation of tuberculous patients receiving antituberculous drugs pointed to the first effective antidepressant strategy through inhibition of the enzyme monoamine oxidase, a strategy applied clinically with the introduction of iproniazid in 1957.

Meanwhile, the search for ever-cheaper, non-hepatotoxic phenothiazines led Geigy to investigate a series of iminodibenzyl derivatives for antihistamine activity similar to that of chlorpromazine. The iminodibenzyl analogue of chlorpromazine, code named G22355, was tested by the Swiss psychiatrist Roland Kuhn but with results later described as 'in some patients, quite disastrous' (Broadhurst, quoted in Healy, 1996) as the drug, although sedative, paradoxically appeared capable of promoting manic-like behaviour. In 1955, Kuhn tried it in depressed patients and in 1957 published results of remarkable effectiveness in 'vital' (endogenous) depression. Imipramine entered use in 1959.

In 1955, the first 'tranquilliser', meprobamate, became available, marketed rather quaintly under the name of the town in which it was manufactured (Miltown), and by 1957 it was the most prescribed drug in the USA. Although safer than barbiturates, it still had a rather unsatisfactory therapeutic index. In 1957, however, Lowell Randall demonstrated the behavioural properties of the 1,4-benzodiazepines, and in 1960, chlordiazepoxide became available in the vanguard of a wave of compounds that appeared to offer, at last, an instant solution to life's worries and the prospect of accommodating the public's concern that anything less than eight hours represents inadequate sleep.

It must have seemed it would go on for ever. But, of course, it did not. For the next quarter of a century or more that would essentially be it – the bubble burst and in the silence after the bang psychiatry was left to ponder, with increasing frustration and some alarm, the inadequacies of the tools with which it had been presented.

This is in no context illustrated better than by the one class of drugs omitted from the above list, and the one that is our major topic of consideration in the present volume – antipsychotics. A brief explanation of how they came to us is of some interest.

The chlorpromazine story

There is no single version of the chlorpromazine story that has percolated through the internecine squabbles about who did what and when and which perhaps inevitably followed such a success involving such disparate players. There are, however, certain indisputable facts in this tale and certain accounts that represent, to use the modern analytical jargon, truth of a more narrative than historical kind. As Mark Twain wrote, 'The older I get, the more vivid is my recollection of things that never happened', and the dramatis personae of this particular production are old men all – or dead. What personal insights can now be offered to resolve the hostilities is unclear.

The following brief account is taken from conventional sources (e.g. Swazey, 1974; Caldwell, 1978; Healy 1996) but to those who, by the revisionist nature of historical endeavour, object to the emphasis, the author presents no defence.

The development of antipsychotics could not have had less to do with the needs of psychiatry. To find their roots, we must first dig in the fertile soil of mid-nineteenth century Victorian commercialism.

The synthesis of mauve from coal tar by William Perkin in 1856 provided the fillip to a whole new industry, commercial dyeing, on the back of which flourished the new specialty of organic chemistry. In 1876, Heinrich Caro, chief chemist of the German company BASF, synthesised a new dye, methylene blue, and in 1883, August Bernthsen, a research chemist, published his analysis of its structure. Bernthsen identified the basic nucleus of methylene blue as 'thiodiphenylamin' or phenothiazine. However, it would take many years and whole new fields of research before this discovery could be brought to its potential.

One area of research was shock, specifically anaphylaxis, which led to the identification of histamine and its actions, while a pertinent strand of pharmacological investigation related to the functioning of the autonomic nervous system. By the 1930s, the existence of acetylcholine and adrenaline had been established. Since antagonists of these naturally occurring amines were known, the pharmacologist Daniel Bovet thought it 'reasonable' to postulate that there might exist substances which interfered with the chemically not dissimilar histamine. In the early 1940s, the French pharmaceutical company Rhone-Poulenc developed a series of synthetic antihistamines, some of which – such as diphenhydramine – are still with us.

Meanwhile, phenothiazine had not been neglected. The antimalarial properties of methylene blue had been established in the 1890s, and subsequently phenothiazine was shown to be an effective insecticide against mosquito larvae. However, the molecule was toxic in humans, though an antihelminthic action against swine ascaria was utilised in

veterinary practice in the 1930s. In the 1940s, the American pharmacologist Alfred Gilman returned to the non-oxidised phenothiazines in search of safe antimalarials, but found these compounds to be ineffective and published his negative results in 1944.

Because of the Second World War, these results did not reach France, where a similar investigation was being undertaken by scientists at Rhone-Poulenc. This investigation succeeded in replicating the negative findings with regard to antimalarial activity, but the French group's interest in the field allowed them to observe what Gilman and Shirley had not – the potent antihistamine activity possessed by a number of these compounds. The most important product of this work was promethazine, produced in 1946.

It was clear that these new synthetic antihistamine compounds had unusual central actions. In humans they were clearly sedative, while some appeared to have beneficial effects in Parkinson's disease. In the autumn of 1950, Paul Koetschet, Rhone-Poulenc's Assistant Scientific Director, proposed a phenothiazine amine development programme, with a view to exploiting central actions irrespective of antihistamine properties. The evidence to support the proposal was flimsy, even by the standards of the time, and Koetschet admitted that it was 'difficult to know' what clinical applications there might be for whatever products emerged. The first he suggested might lie in pre-anaesthesia, while his 'hope' was for more active antiparkinson agents. 'Finally' he mused on the possibility of 'an application in psychiatry'!

Koetschet's reliance on an outcome of interest to anaesthesia was not without foundation, and brings us back to shock. For the first half of the century, the old adage that the operation was a success but the patient died was based on more than gallows humour. Haemodynamic and traumatic shock all too frequently undermined the accomplishments of even the most technically skilled surgeon. Despite a number of explanatory hypotheses, the mechanisms remained arcane. Working within this general framework was a young naval surgeon, Henri Laborit.

Laborit began his research career on a topic of concern to navies the world over – seasickness. His interest was in the possible role of cholinergic mechanisms, and in pursuit of this he and a colleague (Morand) developed a cholinesterase assay for plasma estimations. When, in 1946, it was postulated that inhibition of peripheral cholinesterase may underlie shock, Laborit was well placed to shift his emphasis. He did not accept the primacy of capillary changes in initiating shock, but was more taken with neural (i.e. autonomic) disturbances that might underlie the problem.

Laborit's views on the mechanism of shock and the cocktail of drugs he recommended to counteract it were roundly criticised in later years, but none of this is of relevance to our interest. For what cannot be denied

is that Laborit was possessed of exceptional powers of clinical observation. In obviating shock, his aim was to dampen or 'stabilise' autonomic activity during and after surgery by means of a complex pharmacological regime which latterly included promethazine. This was his so-called 'lytic (i.e. sympatho-parasympatho-lytic) cocktail'.

His observations of the 'secondary' effects of promethazine were impressive, especially in relation to the affective and behavioural changes. He noted that patients became 'calm and somnolent, with a relaxed and detached expression', an effect he was clearly able to distinguish from that of morphine. Laborit's acumen is highlighted by the fact that promethazine had been tried previously in psychiatric patients but only sedation had been noticed.

Much effort has been expended in debating just how pivotal these observations were in Rhone-Poulenc's decision to proceed with the development of aminophenothiazine derivatives, and nothing can be provided here – or perhaps anywhere now – to resolve this controversy. What is fact is that proceed they did; and success came fast. Chloropromazine was synthesised by Rhone-Poulenc's chief chemist, Paul Charpentier, in December 1950, only two months after Koetschet's original proposal, and, after only three months of laboratory study, was deemed ready for clinical trial. The first samples for psychiatric evaluation, as a potentiator of barbiturate-induced sedation, were dispatched to Dr J. Schneider of the Broussais Hospital in April of 1951.

At this time, Laborit was working in the Val de Grace military hospital outside Paris on the development of artificial hibernation as an anaesthetic technique, and he apparantly had no knowledge of the development of the renamed chlorpromazine. When he approached Rhone-Poulenc about the possibility of producing a more effective phenothiazine derivative than promethazine to add to his 'lytic cocktail', he was surprised to learn that one already existed. He received his first samples, as the twelfth investigator, in late June of 1951. In October of that year he was able to report 'the twilight state' that patients entered after receiving his cocktail containing chlorpromazine, and at a meeting the following December he could quote a colleague as observing that the drug 'may produce a veritable medicinal lobotomy'!

Laborit began urging his psychiatric colleagues to try it clinically, although, as the 'urging' was from a surgeon, it is perhaps not surprising that he was met with a fair degree of indifference. In early November 1951, he participated in the first administration of chlorpromazine to a normal subject – his friend Dr C. Quatri, herself a psychiatrist! Quatri described an initial period of discomfiture, supplanted later by 'an extreme feeling of detachment' in which perception was 'filtered, muted'.

In January of 1952, psychiatrists at the Val de Grace finally tried the

drug, although their decision was 'without much conviction'. The patient was a young manic man with several previous admissions. The favourable results were presented orally the following month and published (by Hamon and colleagues) in March. Perhaps because of the origins of their inspiration, the authors of this first published report on the efficacy of chlorpromazine were grudging in their praise, making it clear that 'naturally' they were 'not presenting a new therapy for treating mania'!

However, it was the work of Delay and Deniker that provided the fuel for chlorpromazine's 'lift-off' through a series of reports beginning in May of 1952, although even here it seems that Laborit played a role. According to Swazey, Delay and Deniker heard of chlorpromazine from Deniker's brother-in-law, himself a surgeon, who had utilised Laborit's method.

It is hard to appreciate now how opposed the psychiatry of the time, especially in Continental Europe, was to the idea of pharmacological agents, which were seen as the antithesis of clinical science (Healy, 1996). The 'science' was in unravelling the 'tangled threads' of Bleuler's metaphor. In this context, it is not at all hard to appreciate how frostily the intrusions of a surgeon would be viewed and how, when the trophies were to be awarded, his role would become a source of controversy. But the historical record is clear that it was Henri Laborit, the surgeon, who first identified the psychotropic properties of chlorpromazine. For those offended by the suggestion that he also played a crucial role in providing an impetus for the development of the drug, it is worth recalling that when Rhone-Poulenc came to license the drug to a US manufacturer, they made it clear that they were 'very interested' in ensuring that 'the name and investigations of Dr. Laborit … are mentioned in every scientific publication and also in the popular articles' (Swazey, 1974) – not the recognition conventionally afforded to other than a key player.

As a footnote, however, if we are looking to priority in relation to the start of the modern era of clinical psychopharmacology, this probably belongs to J. Sigwald, who, on the 28th December 1951, started solo chlorpromazine treatment in a 57-year-old chronic psychotic lady – the memorably named Madame Gob!

What, the reader might ask, is the point of all this? It is presented in the belief that those who prescribe chlorpromazine and its successors, who live with their impact and the problems they may cause, and who may even acknowledge the possibility that without them their chosen career might well have been different, may have some interest in the story. It is also presented to dispel the notion, still perpetrated in texts on the subject, that the introduction of chlorpromazine into psychiatric practice was pure 'serendipity'. The drug's development was, no matter

how loosely, a result of the convergence of a number of strands of basic and clinical research with long and honourable scientific credentials, while its eventual home was built on the foundations of astute clinical observation. Its introduction may well have been empirical, but it cannot be considered serendipitous.

There is one final point to highlight from this story – perhaps one of the great ironies of medical history. August Bernthsen, the research chemist who first identified the phenothiazine ring, did so in Heidelberg, only a stone's throw from where Emil Kraepelin would soon formulate his concept of dementia praecox! It would be almost three-quarters of a century before these two powerful developments would find conjunction – years during which psychiatry was dragged through one theoretical quagmire after another and up countless therapeutic blind alleys.

In the wake of chlorpromazine

The pharmaceutical industry was not slow to capitalise on the chlorpromazine story and a series of phenothiazines was soon available. These were, at the end of the day, essentially derivative, with similar modes of action and, as would later emerge, similar sets of problems associated with their use.

The same judgement would apply to the two other drug types that emerged at this time. In 1958, P.V. Petersen, working at the Lundbeck laboratories in Copenhagen, produced the first thioxanthene. This chemical type was characterised by a carbon substitution at position 10 (the R2 position) instead of the nitrogen of the phenothiazines, the effect of which was that side-chains attached by way of a double bond. Thus, these compounds exhibited stereoisomerism, a property that profoundly affected their pharmacology.

Also in 1958, the Belgian chemist Paul Janssen synthesised haloperidol, the first of an entirely new chemical type, the phenylbutylpiperidines or butyrophenones. This was to some extent a fortuitous event as Janssen had been interested in the pharmacological properties of pethidine (meperidine) analogues modified by simple chemical reactions. Haloperidol was the first drug with relatively selective receptor actions, and hence, in terms of general side-effects, had one of the best tolerability profiles. Haloperidol was to go on to become the 'market leader' antipsychotic in terms of volume usage around the world.

Following Kuhn's demonstration of the antidepressant properties of G22355 (imipramine), other heterotricyclic compounds became of interest, and in 1958 the Swiss company Wander began a development

programme of compounds which, like imipramine, comprised a seven-membered central ring structure. One of these, a dibenzodiazepine with an N-methyl-piperazine side-chain, was HF1854, registered in 1960 as clozapine.

Clozapine's success is a story of survival against the odds. Not only were its expected antidepressant actions not evident, but in laboratory animals it did not produce the responses anticipated of an antipsychotic. However, increasing concern about its adverse effects on the granulocyte cell line culminated in 1975 with reports from Finland of a cluster of 13 cases of agranulocytosis, eight of which were fatal. This effectively terminated its development in most countries, but a lingering impression that this drug was something different led to sponsorship of a large multicentre American study of its efficacy and tolerability in a circumscribed patient group resistant to standard drugs. This study (Kane et al, 1988) has become one of the most influential trials in the history of psychopharmacology, and clozapine was the first antipsychotic to which superior efficacy was attributed – albeit in a specific patient population. Furthermore, this and subsequent work pointed to remarkably favourable neurological tolerability.

Clozapine has radically altered perceptions of the mechanisms whereby antipsychotics bring about not only their therapeutic benefits but also their extrapyramidal effects. It has allowed us to break out of the straightjacket of single system psychopharmacology that was the inevitable lure of the classical dopamine hypothesis, and has returned us to something approaching a more realistic appreciation of neurophysiology and brain therapeutics. Clinically useful drugs that were previously denounced as pharmacologically 'dirty' are now rightly viewed as pharmacologically 'rich', and the race to find a 'safe' clozapine has promoted antipsychotic psychopharmacology once again to the first division. This may ultimately come to be seen as clozapine's lasting legacy.

Single system psychopharmacology has not left the scene entirely, however. In the mid-1960s, modification of the substituted 2-methoxybenzamide, metoclopramide, produced sulpiride, which is chemically distinct from other antipsychotics. Although licensed in France in the late 1960s, the efficacy and especially the central pharmacology of sulpiride only came under scrutiny a decade later. It was the first highly selective dopamine D_2 antagonist and hence in effect represented the realisation of the classical dopamine hypothesis as it relates to antipsychotic action. Furthermore, it appeared to demonstrate a dose-dependent separation of effects thought to be predictive of nigrostriatal antagonism (i.e. motor side-effects) compared to those thought to result from dopamine antagonism at mesolimbic sites (i.e. therapeutic effects). This seemed to fit with clinical observations that sulpiride might

possess a lower liability to promote extrapyramidal dysfunction. Accordingly, sulpiride appeared somewhat different from other classes of antipsychotics in both its clinical and pharmacological characteristics, and hence it was the first drug to be referred to as '*atypical*'.

A range of benzamides with a range of indications is now available worldwide. What will become of the antipsychotic benzamides remains to be seen. The 6-methoxy-benzamide, remoxipride, only managed a couple of years before a reported association with aplastic anaemia curtailed its availability, but amisulpride has been available in France for some time, and raclopride has also been reported on favourably. Although enthusiasm for the highly (dopamine D_2) selective approach to antipsychotic development has waned dramatically in recent years, it may be premature to write its obituary just yet. Even 'science' has its fashions!

A new generation of antipsychotic compounds is now emerging. Thus far, all are based on a model extracted from *one* particular aspect of clozapine's 'rich' pharmacology, namely its relatively potent anti-serotonergic – specifically 5-hydroxytryptamine-$_{2A}$ (5-HT_{2A}) – actions. These, in combination with a lower affinity for dopamine D_2 receptors, are behind the designation of these compounds as 'serotonin–dopamine antagonists' (SDAs), although, as with standard drugs, this must not blind one to the fact that they also have many points of pharmacological difference.

This interest in the manipulation of serotonin as a therapeutic aim in psychotic disorders is *re*-newed rather than new, and revives interest of over 40 years ago. These new generation compounds are proving commercially very successful, but it may be that when their place in the armamentarium comes to be more fully established, they will be found to represent relative rather than absolute advances. It is certainly important that we do not substitute one blinkered theory for another and again condemn antipsychotic psychopharmacology to decades of derivative drugs. There are certainly other actions of clozapine awaiting investigation, such as its intriguing and complex effects on noradrenergic systems. There was once a popular theory of that in relation to schizophrenia too, which may one day again see the light of day.

Practice, theory and names

The work of Jean Delay and Pierre Deniker was instrumental in establishing chlorpromazine's therapeutic credentials in psychiatry. They began their investigations in February 1952, unaware of those of Sigwald and Bouttier or the Val de Grace group. Like most early evaluators, their approach was initially towards the drug's use in 'excited'

states, regardless of diagnosis. Thus they, like others, first tried it in mania, although they soon extended it to disturbed patients of other diagnostic types. While they were enthusiastic and found some results that were 'spectacular', the wider psychiatric community was far from ready to be instantly impressed. Indeed, Deniker later recalled how, at the 50th French Congress of Psychiatry and Neurology in July 1952, his talk was scheduled for the last session of the last day, and because of an over-run, was delivered to fewer than 20 people – during the lunch break!

Initial results were, in fact, varied. This was, of course, before randomised and dose-finding clinical trials or operational diagnostic criteria. Application was of the 'try and see' variety – and cautious. The recommended dose from the manufacturer was up to 100 mg per day orally, or a maximum of 25 mg for the first intramuscular (i.m.) injection. Delay and Deniker opted for a 'very high' dose of 75-100 mg i.m. daily plus the same again orally if required, a regime they themselves were apprehensive about. In these early days, Europeans were conservative with regard to dosage. As would be repeated many times with many drugs, it was when chlorpromazine crossed the Atlantic that 'megadoses' entered practice. By the mid-1950s, doses of 1000–2000 mg per day were being used in the USA.

The first British study, reported by Anton-Stephens in the *Journal of Mental Science* in April 1954, was also of the 'try and see' variety, but the major British contribution came from the work of Joel and Charmian Elkes in Birmingham. Their study, reported in the *British Medical Journal* in September 1954, was the first controlled trial of chlorpromazine and one of the first such trials in psychopharmacology. Although providing a qualified confirmation of chlorpromazine's value, they pointed out what Sigwald and Bouttier had also emphasised: that the new drug was not 'curative', but rather produced symptomatic benefits that could be all too quickly lost on discontinuation. The seeds of maintenance were sown early!

Within two years of its announcement to an incredulous, if not hostile, profession, chlorpromazine had achieved international recognition. If this was in the vanguard of something new, however, a new name would be necessary for the class it and its successors represented. Initially, Laborit's influence was again evident in the early suggestions 'neuroplegic' and 'neurolytic'. By 1955, however, two principal effects of these drugs had been established, extrapyramidal dysfunction and so-called psychic indifference, either of which could provide a basis for classification.

The first formal report of extrapyramidal dysfunction appeared in 1954 (Steck, 1954), though the issue had been aired since shortly after the drug's introduction. This aspect of chlorpromazine's use became

increasingly of interest – not concern – because it seemed to point to a possible mode of action. As early as 1953, Delay had stated that parkinsonian effects were dose related. As doses embarked on their relentless march upwards, these effects, unsurprisingly, appeared inevitable. From such an observation it was a short leap of intellect to view them as essential to the therapeutic process.

Thus, within the briefest period, the perception of extrapyramidal disorder shifted from one of adverse to necessary effect. This perception was enshrined in the term neuroleptic, coined by Delay in 1955, which literally means 'seizing' or 'grasping' nerves, and implies a more forceful and fundamental action than 'neurotropic'. The emphasis was therefore very much on the neurological component of action.

What had interested Laborit were the *affective* changes the drug was capable of producing, even after very limited exposure. The word that recurs throughout the earliest writings is 'detachment'. Chlorpromazine did not dull perception, but rather diminished the emotional response to noxious experiences. This was the so-called 'psychic indifference' that translated in behavioural terms into relative composure.

In 1955, the neurologist Howard Fabing and a classicist, Alister Cameron, coined the term 'ataraxy' to cover this phenomenon. It literally means 'without anxiety' or, as Caldwell has more figuratively suggested, 'a state of equanimity'. The drugs promoting this state would then be referred to as 'ataraxics'.

The concept of 'ataraxy' did not catch on, especially in English language psychiatry, although it has resonances in the idea of 'specific sedation' sometimes used, even now, in European psychiatry. It is interesting to speculate why this might have happened. 'Ataraxy' was, after all, a descriptive term for a characteristic mental state effect of drugs whose primary indication was by then mental state disorder. Perhaps psychiatrists had had enough of descriptive psychology, and demanded something that said more of fundamental medical modes of action. Nonetheless, it might be seen in retrospect as a source of regret that the classificatory term to receive universal recognition was one based on a pattern of adverse effects that was not unique, to the exclusion of an alternative that related to the action which set the drugs apart as special in the first place.

In the 1970s, the dopamine theory of schizophrenia was probably the most fertile source of research-testable hypotheses within what was becoming known as biological psychiatry. For some, the drugs from which this theory drew much of its empirical strength became known as 'antischizophrenics'. However, cursory awareness of previous, to say nothing of contemporary, work should have inclined those heading in this direction away from such an elementary error. What almost half a

century of research has made clear is that there is nothing diagnosis specific about the effects of these drugs, at least in terms of the diagnostic categories – the syndromes – we use today.

Where these drugs do appear to exert effects that are relatively unique to them is on symptoms. They seem to act in a direct way against those features we refer to as 'psychotic'. As the means whereby they do this are not merely secondary to sedation, any reference to them being 'tranquillisers', major or any other sort, is both confused and confusing. Increasingly it seems most appropriate that all drugs which share in common these relatively unique actions against psychotic phenomenology should be classified descriptively on the basis of this lead function – i.e. as antipsychotics.

'Typicality' versus 'atypicality'

When everything seemed much the same, there was little incentive for things to be viewed differently. Even recurrent suggestions that sulpiride may have some different pharmacological actions failed to inspire, as the clinical evidence remained equivocal.

The fact of clozapine's difference is, however, indisputable. Hence, the need for a term to encapsulate the fact that this drug is indeed not typical of others in its class. The problem arises when one tries to formulate criteria by which this 'atypicality' can best be conceptualised.

The most obvious criteria are clinical ones, but there is an immediate problem in using clinical parameters. Whatever actions and effects standard antipsychotics have in common are balanced by their differences. What would need to be consistently different in clinical terms for an antipsychotic to be considered in some way separately from its peers?

There are two broad clinical areas (and within these several subcategories) by which antipsychotics might be compared (Owens, 1996). These relate to:

1. efficacy – in terms of:
   (a) acute schizophrenic symptomatology
   (b) long-term maintenance
   (c) negative schizophrenic states
   (d) treatment resistance;
2. tolerability – in terms of:
   (a) general adverse effects
   (b) neurological adverse effects.

There is *no* evidence to date that any antipsychotic compound is possessed of clearly enhanced efficacy in the generality of acute schizophrenic episodes. The concept of 'acute' schizophrenia is at best rather

vague, comprising as it does the major assumption that in states in which florid, productive symptomatology predominates, the underlying pathophysiological disorders – and hence the treatment-response characteristics – are probably the same. Clinical trials of efficacy seldom distinguish first episode patients from those with florid exacerbations of long-standing illnesses, and comparative data of efficacy in these different situations are lacking. Nonetheless, even the data on clozapine do *not* point to its clear advantage in unselected 'acute' cases, although the number and quality of studies are not great (Owens, 1996). It does seem, however, that antipsychotics *cannot* have difference imparted to them on the basis of 'acute' efficacy.

With regard to maintenance, the view is also one of comparability of efficacy for standard drugs, although again formal comparative data are sparse. The evidence for advantage with clozapine in this situation is compelling, with striking improvements in quality-of-life parameters reported over 6 and 12 months (Meltzer et al., 1990; Meltzer, 1992). However, these conclusions do not emerge from randomised relapse-prevention studies but from open studies, in which neither the effects of differential attrition of the less well nor the unique circumstances under which the drug must be administered can be accounted for. It would seem rash to attribute difference on this basis.

Effective treatment of negative states is one of the most pressing requirements in psychopharmacology, and proven efficacy in this area would endow any antipsychotic agent with exceptional properties. There is evidence that such actions can be attributed to certain drugs, such as sulpiride, those SDAs for which we have sufficient data, and especially clozapine. However, the matter is not straightforward and depends, first, on conceptual issues and, second, on issues of clinical acumen.

That schizophrenia is a condition associated with impairment was the cardinal observation that Kraepelin used in delineating this disorder (or group of disorders). Like most of those of his generation, Kraepelin conceived of impairment, or decline, in interpersonal or psychosocial/occupational terms – as something to be identified longitudinally over time. In the era of psychopharmacology, however, practice is much more cross-sectional. The most 'longitudinal' the majority of psychopharmacologists extend themselves to at any one time is the four to six weeks of their current study!

When it comes to encapsulating psychiatry's position on just what are the building blocks of 'negativity', the words of Curren and Mallinson come to mind. In relation to another notoriously difficult concept for psychiatry, psychopathic personality disorder, they stated 'I can't define an elephant, but I know one when I see one'! Even a relatively perspicacious layman 'knows' a negative schizophrenic state when he or

Table 1.2. *The classification of negative features in schizophrenia. (After Carpenter et al., 1985.)*

Primary	Authentic, derived from core illness-mediated pathophysiological disturbance(s)
Secondary	Withdrawal induced by 'positive' symptomatology
	Retardation of depression or other dysphoric mood states
	Psychosocial poverty
	Bradykinesia

she sees one. However, the problems of teasing out the constituent features that comprise this complex state are legion and translate into a glaring lack of professional consensus.

Even if one could define the beast, there remains the very real issue of one's capabilities in determining confidently whether it is of the African or Indian variety – or, for that matter, a hairy mammoth. Many of the features that comprise 'negativity' lack phenomenological clarity and diagnostic specificity. Apparent improvement in negative features might, in fact, reflect improvement in outwardly similar but pathophysiologically quite unrelated phenomena.

In order to address this issue, the idea of 'primary' and 'secondary' negative features was introduced (Carpenter, Heinrichs and Alphs, 1985; Table 1.2), the former being seen as the *authentic* manifestations of the disease process, and the latter term being reserved for similar presentations whose roots are in different terrains. While this is a useful theoretical framework within which to judge clinical observations, it still makes the assumption that it is possible to identify each of these circumstances with confidence in real, living patients. This is a bold and probably spurious assumption, even in relation to any one occurring on its own. It would seem fanciful where two or more are present in the same patient. This point is worth emphasising in light of the prominence given to subjective symptomatology in some of the chapters that follow.

Thus, studies of antipsychotic efficacy in negative schizophrenic states confront Himalayan obstacles. One reviewer concluded that the conceptual and practical difficulties are such that, at present, the question of antipsychotic efficacy in negative states cannot be answered (Moller, 1993). A more pragmatic position might be that, with all of the above taken into account, there is nothing in the literature that is incompatible with the view that reported benefits from antipsychotics lie in the domains of secondary disorder, and hence reflect tolerability rather than efficacy issues. It is important to note that this general conclusion would seem to apply to clozapine as much as it does to other

compounds (Owens, 1996) and, this being the case, it is very likely to apply to the new generation compounds also.

It does not, therefore, appear that antipsychotics can be separated with any confidence on the basis of efficacy in primary or authentic negative states.

The final efficacy parameter on which antipsychotics might be considered for difference is in treatment resistance. In terms of 'positive' symptomatology, the USA multicentre study showed that, by modest criteria, improvements of about 30 per cent could be attributed to clozapine compared to only about 4 per cent to chlorpromazine (Kane et al, 1988). Thus, for the first time, an antipsychotic could be credited with enhanced efficacy – albeit confined to a circumscribed patient group and not radical in degree. Clozapine is not miraculous in this regard, but its effects are sufficiently meaningful for it to be considered atypical of antipsychotics as a whole.

The general tolerability of antipsychotics is hugely diverse and as a rule is not (with one exception) a fruitful sea to trawl in search of difference. The exception is hyperprolactinaemia. Notwithstanding their diverse central pharmacologies, antipsychotics share in common the ability to block the D_2 family of dopamine receptors. This is *the* key fact in our understanding of the pharmacological basis of antipsychotic action. As a consequence of this action on the tuberoinfundibular dopamine system, the standard drugs *all* produce a sustained rise in serum prolactin levels. By contrast, clozapine and most of the newer drugs either produce no elevation of prolactin or only a transient rise.

On this biochemical parameter, clozapine and most new generation antipsychotics are not typical of standard drugs.

Without question, the single major problem associated with the use of antipsychotics is the subject of the present volume: their depressing liability to promote extrapyramidal neurological dysfunction. Any drug with a clearly diminished propensity to cause abnormalities of this sort would certainly be 'different'.

Enter clozapine! To all intents and purposes, acute dystonias do not occur with clozapine; parkinsonism appears to be at most only half as frequent; and a switch to clozapine is associated with 50 per cent or greater reductions in akathisia and tardive dyskinesia ratings. Extrapyramidal tolerability can therefore provide a clear clinical measure of 'difference' (Owens, 1996). As will be emphasised in the following chapters, the position with regard to the new drugs is unclear at the time of writing. These drugs certainly do seem to represent an improvement over standard compounds in terms of a liability to extrapyramidal dysfunction, but, whether collectively or individually, any can truthfully claim the mantle of 'the new clozapine' remains to be seen.

Thus, while the ideal would be to seek 'difference' between antipsychotics on the basis of all of the efficacy and tolerability criteria noted above, only some are at present practical. In clinical terms, the ideal 'atypical' compound should at least have a clearly diminished liability to promote extrapyramidal adverse effects, minimal or no effects on prolactin secretion, and a detectable advantage in the treatment of productive symptomatology unresponsive to standard drug treatments.

The other set of parameters on which difference may be sought among antipsychotics is their pharmacological properties. This in some ways should represent the ideal, although only if at the end of the day it has some meaning in clinical terms. Thus far, this has not proved to be the case. Clozapine's 'rich' pharmacology offers a variety of methods for seeking difference, but these do not have ready clinical resonance. For example, it has been suggested that ratios of receptor-binding affinities to 5-HT_{2A} and D_2 sites may be a useful measure (Meltzer, Matsubara and Lee, 1989), and in this regard clozapine is certainly different, having a higher ratio than other established compounds. However, by this criterion, risperidone should be highly atypical as it has one of the highest ratios of all the available drugs, yet clearly enhanced efficacy in treatment resistance remains to be established and clinically its use is associated with a dose-dependent increase in prolactin secretion and in extrapyramidal side-effect (EPS) liability.

One established property of the standard drugs is the development of post-synaptic supersensitivity of D_2 dopamine receptors with chronic exposure. This phenomenon does not apparently occur with chronic exposure to clozapine (LaHoste et al, 1991), while chronic treatment with remoxipride is associated with upregulation (an increase in numbers) but not apparently with functional supersensitivity (Ogren et al, 1990). Remoxipride does appear to have a reduced EPS liability compared to the high-potency haloperidol, but, in comparison with other low-potency drugs, its position is less clear (Owens, 1996). Whether the ability to produce functional supersensitivity with chronic exposure is a valid basis for a dichotomous classification of antipsychotic drugs remains to be seen.

'Atypicality' is a valid concept in view of the unique clinical and pharmacological properties of clozapine but, until differences in both these areas can be meaningfully connected, it should be used with circumspection. Most importantly, 'atypical' should not be seen as a synonym for 'new'.