What's in a name? The evolution of the nomenclature of antipsychotic drugs

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Objective: Psychiatry as a science and psychotherapy as an art thrive on words, words that were often coined arbitrarily and that are often used idiosyncratically. This article examines the origins, progenitors and usage of the word "antipsychotic" and explores its ramifications. **Methods**: Original publications from the 1950s onward, beginning with the report of the discovery of chlorpromazine, were sought for their specific references to the terminology of drugs used to treat psychotic disorders. Preferences for individual words, debates surrounding their adoption and changing trends in their use are reviewed from scientific, clinical and social perspectives. **Results**: Over the past 50 years the drugs used in the treatment of schizophrenia and other psychotic disorders have been variously labelled "tranquillizers," "neuroleptics," "ataractics," "antipsychotics" and "anti-schizophrenic agents." These terms, coined out of necessity, were quickly accepted with little debate or due consideration of their clinical, personal and social implications. The development of a new generation of antipsychotic drugs as well as the prospect of treatment strategies with diverse mechanisms of action highlight the need to re-examine the issues involved in the naming, classification and labelling of psychotropic drugs in general and of "antipsychotics" in particular. **Conclusion**: This historical overview of the labelling of drugs used in the treatment of psychoses reflects the confusion and controversy surrounding the naming and classification of drugs and diseases in general. It also illustrates the dynamic interplay of personal beliefs, rational thinking, practical considerations and societal values in shaping the scientific process.

Objectif : La psychiatrie comme science et la psychothérapie comme art se nourrissent de mots, souvent créés arbitrairement et souvent utilisés de façon idiosyncratique. Cet article analyse les origines, les antécédents et l'usage du mot «antipsychotic» (antipsychotique) et en explore les ramifications. **Méthodes** : On a cherché des publications originales à compter des années 1950, à commencer par le rapport sur la découverte de la chlorpromazine, pour y trouver des renvois précis à la terminologie des médicaments utilisés pour traiter les psychoses. On a étudié les préférences manifestées à l'égard de certains mots, les débats entourant leur adoption et l'évolution des tendances de leur utilisation des points de vue scientifique, clinique et social. **Résultats** : Au cours des 50 dernières années, les médicaments utilisés pour traiter la schizophrénie et d'autres psychoses ont porté divers noms : «tranquillizers» (tranquillisants), «neuroleptics» (neuroleptiques), «ataractics» (ataraxiques), «antipsychotics» (antipsychotiques) et «anti-schizophrenic agents» «agents antischizophréniques». Ces termes issus de la nécessité ont été acceptés rapidement après des débats limités au cours desquels on a peu réfléchi à leurs répercussions cliniques, personnelles et sociales. La

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mise au point d'une nouvelle génération de médicaments antipsychotiques, ainsi que les perspectives de stratégies de traitement ayant divers mécanismes d'action, démontrent qu'il faut réexaminer les enjeux intervenant dans la dénomination, la classification et l'identification des psychotropes en général et des «antipsychotiques» en particulier. **Conclusion** : Cette rétrospective historique de l'identification des médicaments utilisés pour traiter les psychoses traduit la confusion et la controverse qui entourent la désignation et la classification des médicaments et des maladies en général. Elle illustre aussi l'interaction dynamique entre les croyances personnelles, la réflexion rationnelle, les considérations pratiques et les valeurs de la société dans l'orientation du processus scientifique.

Introduction

The growth of modern English vocabulary has been attributed to 4 main factors: the acquisition and assimilation of new words encountered by English speakers in the process of colonizing other nations; increases in travel, trade and immigration; advances in science and technology; and cultural and social development of speakers of the English language.[1,2] Psychiatric lexicon and nomenclature have experienced a comparable evolution. In the early part of the 20th century the vocabulary of this scientific discipline was enriched by the birth of psychoanalysis, and this trend continued into the era of psychopharmacology.[3,4] Although the term "psychopharmacology" was introduced some time ago, the early psychotropic armamentarium was limited to a very few compounds, such as the bromides, the barbiturates, chloral hydrate and the opiates.[5-7] As Macht[5] remarked in 1920 (p. 167): "The number of contributions to the domain of what we may be permitted to call psychopharmacology is certainly very meagre."

This situation changed in 1952 with the introduction of chlorpromazine, a phenothiazine compound synthesized by the French chemist Paul Charpentier and presented to psychiatrists by the surgeon Henri Laborit. The interesting story of the discovery, early clinical uses and history of chlorpromazine has been well presented by others[6,8-10] and will not be repeated here. Instead, this article is limited to a focused investigation of the words used to describe the new class of drugs, which were quickly seen to be different from known sedatives and which were subsequently used almost exclusively for the treatment of schizophrenia and other psychotic disorders. Today, we routinely refer to the first generation of these drugs (e.g., chlorpromazine, haloperidol and thioridazine) as "antipsychotics" or "neuroleptics" and to the newer, second-generation medications (e.g., clozapine, risperidone and olanzapine) as "atypical antipsychotics." But during the 1950s, 1960s and early 1970s there was considerable debate over what terminology and classification were appropriate to distinguish and describe these newly developed compounds. These arguments went well beyond semantics, to consider the implications of nomenclature vis-à-vis proposed causes and mechanisms of schizophrenia and other psychoses. An early example of this debate is found in the proceedings of the Psychopharmacology Symposium held in 1957 during the second International Congress of Psychiatry in Zurich. At that meeting the Canadian psychiatrist Heinz Lehmann chaired a discussion on terminology, asking the following specific questions:

- What should the drugs that we are talking about be called?
- What do the drugs do in terms of their clinical action?
- Are they curative or palliative?
- How should we refer to their clinical effects?

A lively debate followed, with various proponents putting forth their favourite terms. A survey of the participants' comments reveals the relative popularity of the then-current terms. At that time, "neuroleptic" was the most widely used term, followed by "tranquillizer" and then "ataraxic."[11] Since the early 1970s the debate has died down, to the point of virtual silence, even though more drugs are used today in the treatment of psychotic disorders than ever before. Still, the words we use to name the drugs seem to have made their way into general usage not by a process of critical debate, but merely by chance.

The debate over what to call the new drugs being used in the treatment of psychoses, a debate that started in the early days of psychopharmacology, should therefore be reopened for the following reasons. First, nomenclature has an impact on health care practitioners: the terms we use have a profound effect on how we view these medications, how we think they work, what we think their effects are and how we think they differ from other similar medications. These

perceptions represent physicians' beliefs and attitudes and are reflected in their prescribing habits. Second, nomenclature has an impact on drug consumers: the terms we use may imply adverse social connotations of which our patients are more aware than we are. Third, psychopharmacology is growing rapidly, and we face the prospect of a new generation of antipsychotic drugs whose novel mechanisms of action and scope of use will radically alter conventional thinking and clinical practice and present special challenges. Thus, a review of the past arguments and theories evoked in the proposed naming and classification of these drugs is essential to properly address issues related to the conceptualizing, categorizing and naming of the newer generation of compounds to be used in the treatment of schizophrenia and other psychotic disorders.

The early terms "tranquillizer," "ataractic" and "neuroleptic"

From its early uses, chlorpromazine was observed to produce a calming effect on mentally disturbed patients, without oversedation and without impairment of consciousness, which were problems with the other central nervous system depressants known at that time. One of the first words used to reflect this effect was "tranquillizer,"[8] a term whose first use in the English language is attributed by the *Oxford English Dictionary*[12] to the English novelist Fanny Burney in her journal of 1800: "I find, however, useful employment the best tranquiliser, and ... I have less of the violent emotions which have hitherto torn..." The first recorded medical use of the word was by E. Sutleffe in 1824: "I invited the attention of the medical world by introducing this herbaceous tranquillizer (sc. ground ivy) to their notice."[12] The first naming of chlorpromazine and reserpine as tranquillizers is attributed (by Hoffmeister and Still[13]) to Yonkman.

In 1955 another term, "ataraxic," was proposed. Caldwell[8] made the following remarks about this term:

> The word ataraxy became a psychiatric term in 1955 when Fabing together with Cameron who is a professor of classics named chlorpromazine-like psychotropic drugs "ataraxics" and their action "ataractic" — derived from the Greek adjective *ataraktos* meaning "not disturbed, not excited, without confusion, steady, calm" or from the verb *ataraktein* "to keep calm."

Caldwell then went on to differentiate major from minor ataraxics in the same way that we currently distinguish major from minor tranquillizers, the former being effective in psychoses and the latter in neuroses.

The terms "tranquillizer" and "ataractics" seem to have been quite popular in the 1950s[11] but are rarely employed today.[14] There are various reasons for this change in usage. In the 1960s and 1970s many psychiatrists felt that these drugs did not actually produce feelings of calmness or happiness but had a more specific effect on a patient's psychosis.[3,15,16] To some, the word "tranquillizer" may have implied a degree of manipulation and control. In his 1957 article, Szasz[17] said that such medications treated the patient's behaviour and not the illness, thus benefiting the health care worker more than the patient. He likened the relatively new tranquillizing drugs to chemical straitjackets.

"Neuroleptic" proved a more lasting term. It was proposed in January 1955 to the Académie nationale de médecine by Jean Delay and Pierre Deniker to describe the specific neuropharmacologic effects of chlorpromazine. Deniker stated that it was derived from the ancient Greek and meant "which takes the nerve."[10] The concomitant neurologic effects include the parkinsonian features of rigidity, bradykinesia and tremor, but also encompass the "neuroleptic syndrome," consisting of the "suppression of spontaneous movements and complex behaviour while spinal reflexes and unconditioned nociceptive–avoidance behaviours [remain] intact."[18]

"Neuroleptic" was, and still is, a popular term. But is it appropriate? Various critics have expressed their doubts. For example, in 1969 Kline[19] mentioned the following concern (p. 292):

> Delay and Deniker in their original publication referred to chlorpromazine as a "neuroleptic" because it produced extrapyramidal symptoms. The rest of the universe classifies chlorpromazine and other phenothiazines and phenothiazine-like drugs by the antipsychotic effect they have on the psychological state of the user. ... Why the system should be disrupted by the inclusion of one category based on neurological side effects is difficult to comprehend.

In 1989, Deniker[10] himself reminisced (p. 256) as follows:

> [The] Americans were horrified — think of it: it was a matter of defining a group of drugs by their adverse effects — and they preferred such terms as "tranquilizers", later on using the expression "major tranquilizers" and finally using the expression "antipsychotic."

One of the reasons for the persistence of the term "neuroleptic" may have been that the neurologic side effects of chlorpromazine and related drugs were linked empirically to their efficacy in treating agitated states.[10,16] Many practitioners even recommended increasing the dose of the medication until extrapyramidal effects became apparent.[15] One wonders whether the term itself, "neuroleptic," perpetuated this idea. The theory connecting antipsychotic efficacy with neurologic side effects was questioned in 1964 when a double-blind, placebo-controlled study comparing the effects of chlorpromazine, fluphenazine and thioridazine showed that although thioridazine was associated with a lower incidence of neurologic side effects, its antipsychotic efficacy was equal to that of the other drugs.[15] Later on, when clozapine, which was very effective in the treatment of schizophrenia, was shown to have no extrapyramidal effects, even more doubt was cast on the hypothesis.[10,14] Lehmann and Ban,[14] citing Ackenheil and Hippius, made the following suggestion (p. 157):

> The launching of clozapine for clinical use was delayed, even in Europe until 1972 ... because the findings challenged the commonly held belief of a close relationship between antipsychotic effects and extrapyramidal disturbance.

Introduction of a new term: "antischizophrenic"

A National Institute of Mental Health (NIMH) study published in 1964 suggested that drugs such as chlorpromazine, fluphenazine and thioridazine have specific actions against the symptoms of schizophrenia apart from the mere tranquillizing effect used to control the behaviour of obviously agitated patients.[15] These included improvements in the areas of confusion, tension, auditory hallucinations, self-care and social participation. The NIMH study[15] went so far as to state the following (p. 257):

> Almost all symptoms and manifestations characteristic of schizophrenic psychoses improved with drug therapy, suggesting that the phenothiazines should be regarded as "antischizophrenic" in the broad sense. In fact, it is questionable whether the term "tranquiliser" should be retained.

But Shepherd[20] pointed out that "drug action can only be taken as 'anti-schizophrenic' if the symptomatology of schizophrenia be equated with the disease process" (p. 101). At any rate, use of the term seems to have been short-lived.

Yet another term: "antipsychotic"

Until the mid-1960s, it seems that there was some reluctance to admit that phenothiazines were anything but tranquillizers. Lehmann,[6] remembering the early use of chlorpromazine in the 1950s stated, "neither I, nor [clinicians in the United States] dared to attribute specific antipsychotic effects to these drugs" (p. 300). Lehmann, in fact, may have been one of the first psychiatrists to use the term "antipsychotic," or at least he later believed himself to have been the first, saying, "In 1956, when I was addressing the Canadian Medical Association, I introduced the term 'antipsychotic' apologetically, and more as a metaphor than a designation" (p. 300).[6]

Today, "antipsychotic" seems to be the most popular term applied to drugs — both new and old — used to treat psychoses, and it has been advocated by some prominent psychopharmacologists.[18] Indeed, the term is so general and widespread that it has been difficult in this paper to avoid inadvertently using it to describe the category of drugs under discussion. The term is descriptive enough to distinguish the medications it denotes from "tranquillizing" drugs such as the benzodiazepines, yet general enough not to imply that these medications have an action involving the hypothetical causes of the conditions they are used to treat. Still, arguments similar to those against the term "antischizophrenic" have been directed against "antipsychotic." Poldinger (quoted by Shepherd[20]) made the following points:

> The designation "antipsychotic" does not mean the causal action on psychotic states: however, the term is supposed to describe an action which is more than the total of its partial effects on individual symptoms. The expression "more than the total" is reminiscent of the so-called "Gestaltpsychologie."

In a sense, however, this vagueness may not be the fault of the term itself but of the discipline that created it. In a book on neurochemistry, Toman[21] said it this way (p. 729):

> Most classifications for didactic purposes are hybrid, traditional, colourful and misleading. The chief reason for this unsatisfactory state of affairs is the relative poverty of knowledge concerning mechanisms, either at the cellular or molecular levels of explanation, which would give a sound theoretical base for systematizing drugs.

Participants in the discussion at the 1957 International Congress of Psychiatry mentioned above also realized that a terminology based on the clinical effects of a drug was bound to be vague and undesirable, although perhaps unavoidable. As H.H. Meyer (quoted by Kline[19]) put it, "We know perfectly well that psychiatric classifications prevail just now, and we shall have to wait for further theories and further observation in order to come to a more precise and better grouping."

"Atypical antipsychotics" and classification of drugs by receptor affinity profiles

In the meantime, we now know more about the cellular and molecular mechanisms of so-called antipsychotic drugs, but this seems to have resulted in more rather than less confusion about how they should be named. Earlier compounds are often identified as dopaminergic blocking drugs, whereas the new arrivals such as olanzapine, risperidone and quetiapine are being categorized as serotonin–dopamine antagonists. But even these classifications are not always consistently applied. The concept of atypicality is still evolving, and several defining characteristics have been proposed.[22,23] As Kane and colleagues[22] wrote, the concept of atypicality is a working concept rather than a well-delineated and validated criterion of classification. The concept was first put forward by Stille and Hippius[24] in the context of comparing the efficacy and lack of extrapyramidal symptoms of clozapine with those of what were known as classical antipsychotics. Recently, Lieberman[23] (p. 36) has elucidated the clinical properties that define the atypical antipsychotics:

- They must have efficacy against the psychotic symptoms of schizophrenia.
- They should provide some measure of superior efficacy against positive symptoms in patients who have not previously responded to conventional antipsychotics, against primary and/or secondary negative symptoms, or in the amelioration of neurocognitive deficits that impair the ability of the schizophrenic patient to think and function.
- They should cause little or no symptomatology of acute extrapyramidal symptoms (parkinsonism, acute dystonia, or akathisia) or of tardive dyskinesia.
- They should not elevate prolactin to the degree that may result in endocrine side effects, such as oligomenorrhea or galactorrhea.

Obviously, some of the newer antipsychotic agents fit this definition (e.g., clozapine and perhaps olanzapine), while others do not (e.g., risperidone, which does affect prolactin production). Likewise, some of the older conventional antipsychotics such as thioridazine and loxapine have also been regarded by some researchers as atypical because of the relatively low incidence of extrapyramidal symptoms and the discovery of high 5-HT_2 receptor blockade.[25,26] This dilemma illustrates an important observation by Sollman (as quoted by Shepherd[20]), that systems of classifying drugs by their systemic actions are often unsatisfactory because the pharmacologic action — in this case serotonin or dopamine receptor blockade — may not always be consistent with the therapeutic actions — the "antipsychotic" and anti-extrapyramidal symptoms:

> For this reason it would not be advisable to classify drugs strictly according to their pharmacological actions. On the other hand, a therapeutic classification is not favourable to a study of the underlying actions of the drugs, and tends to empiricism.

"Novel" and "second-generation" antipsychotic agents

Two other terms, "novel" and "second generation" have been used in recent publications to identify the newer antipsychotic drugs, usually by distinguishing them from typical, conventional or traditional antipsychotics. Quite often, the older antipsychotics are referred to as "neuroleptics." This opens up the possibility of many combinations and permutations.

A text word search of MEDLINE for the period 1960 to 1999 revealed the following citation frequencies in the psychiatry, chemistry and pharmacology literature: 647 instances of atypical antipsychotic, 325 of atypical neuroleptic, 166 of novel antipsychotic, 18 of serotonin–dopamine antagonist, 11 of second-generation antipsychotic, none of second-generation neuroleptic, none of first-generation antipsychotic, 126 of typical antipsychotic, 124 of typical neuroleptic, 63 of conventional antipsychotic, 52 of conventional neuroleptic, 25 of traditional antipsychotic and 20 of traditional neuroleptic.

A number of conclusions can be drawn from these findings. First, over that 39-year period "antipsychotic" was, overall, a slightly more popular term than "neuroleptic," even to describe the older drugs. Second, for some reason the term "atypical neuroleptic" is in common use, although the definition of "neuroleptic" itself logically excludes the concept of atypicality. There are

even more complex combinations to be found (not listed above) such as "atypical antipsychotic neuroleptic"[27] and "novel atypical antipsychotic."[28] The latter is just a matter of combining 2 adjectives, whereas the former poses some fundamental questions of definition.

What do we really mean when we use these terms? There is an underlying assumption in medicine that "everybody knows what we mean," but should these basic principles be left to intuition or guesswork? To our knowledge, aside from "atypical antipsychotic," none of the terms listed above has been explicitly defined.

Discussion

Looking back over the history of the drugs used to treat psychoses, it appears that the terms used to name them most often reflect therapeutic actions rather than pharmacologic properties or biochemical profiles. This tendency extends to the naming of the newer drugs, more often termed "atypical antipsychotics" than "serotonin–dopamine antagonists." There is now a large collection of names used to refer to these medications, and, as in the past, their entry into the common vocabulary of psychiatrists, pharmacologists and other professionals has been a matter of chance rather than the result of informed discussion and debate. Psychopharmacologists seem to prefer more exact terminology and definitions, as illustrated again at that historic meeting of scientists at the second International Congress of Psychiatry in Zurich. There, Margolis (as quoted by Kline[11]) made the following recommendation:

> Until we have more complete knowledge of the mode of action of these drugs and until we can be more specific regarding what we mean when we employ such epithets as "tranquilizers," "neuroleptics," "ataraxics," etc., I would propose that insofar as is possible we adhere to exact pharmacologic terminology. In speaking of specific drugs such as reserpine, the phenothiazine derivatives, meprobamate, etc., nothing is more clear than these very terms.

But today, who besides a psychopharmacologist refers to risperidone as a thienobenzodiazepine or a benzisoxazole derivative? Margolis continued as follows:

> When referring to this group of pharmacologically diverse substances as a whole we can use only general designations, and those which are chosen must be *left undefined and bracketed by quotation marks* [emphasis in original]. In doing otherwise the psychopharmacotherapist is guilty of perpetuating scientific inexactitudes in which diverse and incompletely understood mechanisms are described in vague and nebulous language, and he would court the same criticism which fell the way of the psychoanalytic schools which invented a vocabulary peculiar to and understandable only to themselves.

However, such criticisms have appeared only rarely in the intervening 45 years. Regulatory agencies such as the US Food and Drug Administration and Health Canada's Therapeutic Products Programme (now the Therapeutic Products Directorate) have ruled that all medicinal products should be clearly labelled and identified by their primary indication at the time of dispensing.[29] This requirement is clearly important for facilitating an open and informed treatment process, but there are a number of potential problems in following this principle.

First, inadequate knowledge about the nature of mental illnesses and the mode of action of antipsychotic drugs indicate that premature labelling could be meaningless, if not positively misleading. An antipsychotic could be simply described as a drug that is used to treat psychosis, though the definition and scope of the word "psychosis" itself remains unclear. Although reality distortion characterized by hallucinations and delusions is considered the core feature of psychosis, its exact relation to the other dimensions of psychopathology, such as negative symptoms, cognitive deficits, and other ancillary symptoms — in other words, the boundaries of psychosis — is yet to be established.

Second, the interrelations between the biochemical profiles of antipsychotic drugs, their pharmacologic actions in controlled experimental studies and the diverse therapeutic uses to which they are put in clinical settings are even more complex than was originally presumed. There is a growing trend in psychiatric practice to use the same medication for different purposes in different clinical settings. For example, recent clinical studies indicate that newer antipsychotics such as olanzapine may possess mood-stabilizing effects and could be useful in treating mood disorders such as bipolar disorder.[30] On the other hand, drugs from diverse pharmacologic backgrounds may be used to achieve a common therapeutic goal, for example, the use of both cholinesterase inhibitors and glutamatergic compounds in the treatment of the same psychotic disorders.[31] These observations raise some fundamental questions about the scope of the term "antipsychotic."

The Food and Drug Administration has recently acknowledged this dilemma and has attempted to redress the issue by allowing these drugs (e.g., olanzepine) to be labelled "psychotropics" instead.[32]

The scope of this discussion clearly extends beyond simple linguistics into the realm of clinical practice, raising subtle ethical dilemmas as well. For example, many clinicians know that attempts to obtain informed consent for antipsychotic drug therapy from a person with little insight into the nature of his or her illness provokes a predictable response: "Why do I need this pill, doctor? I'm not a psychotic!" Often it seems that such people are more receptive to being told that the medications may help to relieve their fear and anxiety. Although this may be true, it is obvious to the physician that the drugs in question are not in the same class as anxiolytic medications such as the benzodiazepines.

Third, as Szasz has pointed out, there is a stigma attached to certain names used for psychotropic medications.[17] Admission that one is taking cholesterol-lowering agents may be quite acceptable in cocktail conversations, but the mere mention of receiving antipsychotic drugs could jeopardize the speaker's chances of getting a job or entering into a relationship. Besides, the chore of taking antipsychotic pills on a daily basis over prolonged periods serves as a constant reminder of the original illness and the unpleasant experiences surrounding it, which perpetuate self-stigmatization, self-doubt and low self-esteem.

All of these points should be taken into consideration when naming classes of medications for the psychiatrically ill, especially those with psychotic conditions. Labels have had powerful connotations in the field of psychiatry, and their profound personal and social significance should never be underestimated. Meanwhile, a confusing array of terms remains in use, perhaps for lack of a better alternative. Also, it becomes evident that the confusion and controversy surrounding names is attached not only to antipsychotic drugs, but also to the illnesses that they are intended to relieve!

This chaos is frustrating, and consensus would be comforting. The temptation to judge individual terms, force unanimity, consider alternatives and even coin new labels is always present. However, the purpose of this overview has been to provide factual information to readers who might not have had a chance to appreciate the evolution of the various terms for medications used in the treatment of psychotic disorders.

Conclusions

Despite the well-known Shakespearean saying, "What's in a name?" the task of naming has always been both difficult and important. Naming serves several functions in science as well as in social settings. Compared with the situation in other branches of medicine, naming has proven especially crucial in the field of psychiatry. It is ironic that psychiatry has come so far in elucidating the biochemical nature of psychoactive medications and is using this knowledge to develop newer and better drugs to treat psychoses, while it has allowed history to repeat itself in the vagueness of drug nomenclature and their systems of classification. Today, the neuroleptic–ataraxic–tranquillizer conundrum has merely been replaced by the atypical antipsychotic – novel antipsychotic – serotonin–dopamine antagonist confusion. In 1957, Jacobsen suggested at the second International Congress on Psychiatry "that in future publications everyone should use the word they like until an international use has been fixed."[11] Four decades later, everyone is still doing just that!

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