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A patient-centered model of the action of psychotropic drugs

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ABSTRACT

Background: Psychotropic medications are widely used to treat a variety of mental disorders, but a unifying explanation of their modes of action remains obscure.
Objective: To examine the limitations of existing models of psychotropic drug action, and to propose an integrative, patient-oriented model that explains the wide spectrum of actions of psychotropic medications.
Method: The traditional "disease-centered" model of psychotropic action, and its most logical contemporary alternative, the "drug-centered" model – are critically analysed, and their limitations identified. An alternate model, which acknowledges the importance of patient-related factors in determining drug effects is outlined. The two processes involved in this model, and the evidence in its support, are explained at length with reference to specific psychiatric disorders.
Conclusion: The patient-centered model proposed in this paper, though provisional, provides a broad-based, unified framework for understanding the actions of psychotropic drugs, and can enhance clinical practice and research.
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1. Introduction

Psychotropic drugs are widely used in the management of several mental disorders. In some conditions, such as schizophrenia [1] and bipolar disorder [2], medications are the treatment of choice. In others, such as depression [3], these drugs are often used in combination with psychological therapies, or as an alternative to them. The widespread availability and apparent effectiveness of these drugs has led to widespread increases in their use, even in "special" populations such as children [4], pregnant women [5] and the elderly [6].

Concerns have been raised about the wisdom and safety of using psychotropics in this manner [7]. Besides obvious concerns about the long-term physical adverse effects of these drugs [8–11], researchers have also identified paradoxical, unwanted and dangerous effects on behaviour in some patients [12–14]. This has led to restrictions on their use, especially in children and adolescents [15]. However, other patients experience responses that go beyond the therapeutic, including apparently desirable changes in deep-seated patterns of feeling and behaviour [16,17]. This wide range of effects caused by psychotropics naturally leads to a consideration of the mechanisms involved, and the factors that can modulate them.

1.1. Pharmacodynamics, efficacy and safety of psychotropics

At the cellular level, all psychotropic drugs act by altering the actions of one or more neurotransmitters. For example, tricyclic antidepressants act by blocking the reuptake of monoamine transmitters – noradrenaline and serotonin – from the synaptic cleft, leading to increases in their levels [18]. A wide body of research work has examined how psychotropics affect individual transmitters [19], receptors [20], second messengers [21], genes [22], and other key components involved in intra- and inter-cellular signalling [23]. Recently, it has been found that antidepressants have the ability to improve connectivity (synaptic plasticity) between neurons [24]. These molecular and cellular actions have been demonstrated both in experimental animals and in humans, and are presumed to underlie the therapeutic benefits seen with these drugs.

Similarly, the adverse effects of psychotropics can often be explained with reference to their actions on specific neurotransmitters and receptors. For example, most available antipsychotics

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block dopamine type 2 (D2) receptors in the nigrostriatal pathway of the brain, producing signs and symptoms that resemble Parkinson's disease. This condition is known as drug-induced Parkinsonism [25].

However, when it comes to considering how a drug molecule can affect a complex behavioural syndrome – such as depression or schizophrenia – molecular and cellular explanations are often inadequate. While research has found evidence of various neurotransmitter, neuroendocrine or cellular abnormalities in mental disorders, these are best understood as "correlates" of these conditions. The search for a unifying biochemical "cause" or "model" for any psychiatric disorder has not yielded conclusive answers.

To state this in another way: If a neurotransmitter imbalance, or cellular-level defect, were the cause of a mental disorder, then all, or at least most patients would respond to a drug which corrected it in some way. If, on the other hand, the molecular-level abnormality had nothing to do with the disorder in question, drugs would not work at all, or would work only as "active placebos" – their response rates would approximate those of an inert drug ("placebo"), but they would cause adverse effects which could be predicted from their pharmacological actions.

Results from real-world drug trials suggest that the truth lies somewhere between these two extremes. A sizeable proportion of patients – between 40 and 70% - experience a significant reduction in their symptoms when taking psychotropics [26,27], and a smaller percentage (around 30% in the case of depression) experience a complete remission [28]. While placebo response rates are high, there is enough evidence to suggest that psychotropics outperform placebos in several conditions. These include schizophrenia, severe depression, bipolar disorder, obsessive-compulsive disorder (OCD), and several anxiety disorders. However, none of these drugs "cures" the underlying disorder, and symptoms tend to recur when they are discontinued. A further point of interest is that the response rates quoted above are statistical aggregates, which encompass a wide range of responses in individuals, ranging from dramatic remissions to a complete failure to respond. These individual differences are obscured by the emphasis on aggregate measures, such as response and remission rates, in most clinical trial reports.

In addition to these results, the phenomenon of "behavioural toxicity", in which a psychotropic drug causes undesirable behavioural effects, is difficult to explain. A classical example, already alluded to above, is the paradoxical occurrence of suicidal behaviour or violence in children or adolescents receiving a selective serotonin reuptake inhibitor (SSRI) for depression [14,29,30]. Such effects are clearly not direct consequences of the drug's neuropharmacology alone. If they were, they would be more common and predictable, and perhaps show dose-response relationships, as in the case of drug-induced Parkinsonism. In pharmacological terms, behavioural toxicity is a "Type B" adverse effect [31] – an idiosyncratic phenomenon that depends on mechanisms that are peculiar to the recipient, similar to an allergic drug rash.

A third phenomenon that requires explanation is the broad "spectrum of efficacy" seen with several of the available psychotropic drugs. Quetiapine, for example, is marketed as an antipsychotic – that is, a drug for patients with schizophrenia. Despite this, it also has "anti-manic" [32] and "anti-depressant" [33] properties. The SSRI antidepressants, such as fluoxetine, are also "anti-anxiety" [34] and "anti-OCD" drugs [35] of proven efficacy. In other words, drugs are often not specific for a given disorder: they seem to work in a wide range of psychiatric disorders, some of which are quite different. At times a drug works in particular conditions at different doses: for example, risperidone is an antipsychotic at regular doses, but helps patients with OCD at much lower doses when added to an SSRI antidepressant [36].

In order to explain the wide range of responses that can be seen in a given patient receiving a psychotropic drug, factors other than the drug itself need to be considered, and incorporated into a broad explanatory framework – a "model" of psychotropic drug action. In the following section, the necessary components of such a model are outlined.

1.2. "Disease-centered" and "drug-centered" models of psychotropic action

Before describing this model, it is worth considering two models of psychotropic drug action that have been discussed in the literature. Following terminology that was proposed by Moncrieff and Cohen [37,38], they can be referred to as the "disease-centred" and "drug-centred" models, respectively. Both have their strengths and weaknesses, which are outlined below.

The "disease-centred" model is the one that most practicing psychiatrists are familiar with. According to this model, drugs exert disease-specific actions; they directly or indirectly control or correct the putative biological abnormalities associated with a particular condition, such as depression. Under this model, terms like "antidepressant" and "antipsychotic" – which are in common use – are considered accurate and appropriate, and any overlap in their effects is ascribed to a possible "neurobiological overlap" between the conditions in which these drugs work. In a modified form, this model has gained some popularity with the public, and it has had a significant influence on the principles and practice of psychiatry [39,40]. However, it fails to explain the three phenomena described in the previous section – the variability of response, the non-specificity of certain psychotropics for particular disorders, and behavioural toxicity.

A plausible alternative to this model is what Moncrieff and Cohen have termed the "drug-centered" model [37]. According to this view, psychotropics do not exert "disease-specific" actions at the molecular or cellular level. Instead, by altering brain transmission and activity, they produce an "altered" or "abnormal" state of brain activity. The term "abnormal", here, is not a value judgement but a statement of fact – psychotropics alter brain physiology and chemistry. This "abnormal" state can, through mechanisms that still await clarification, be therapeutic in some people, toxic in others, and produce an entire spectrum of changes in different recipients. An extreme version of this model, proposed by Breggin, focuses on the undesirable effects of psychotropics [41,42]. This view can be summed up in the following statement: "All biopsychiatric treatments share a common mode of action – the disruption of normal brain function. None of them improve brain function" [41]. Even if such categorical statements are avoided, the "drug-centered" model has an elegance that the standard model lacks. It explains one puzzling phenomenon encountered above: the "broad-spectrum" properties of some psychotropics. Since the mode of action of these drugs, under this model, is merely the induction of an "abnormal brain state", such a state could have positive effects on a variety of mental disorders, rather than on a single diagnostic entity. However, like the "disease-centered" model, it does not fare as well in explaining the variations in response seen with a given drug – as the presumed "abnormal state" must be the same, or similar, in most patients receiving the drug, why should responses vary so widely? It also fails to explain the occurrence of rare, "type B", behavioural toxicity events.

2. A patient-centered model of psychotropic drug action

A valuable step towards a better model was outlined by van der Gaag, in a paper dealing with the remission of certain symptoms of schizophrenia [43]. Starting from a bio-psychological perspective,

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