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## Analysis

### How do psychiatric drugs work?

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*Joanna Moncrieff and David Cohen argue that changing our view of the action of psychiatric drugs would help patients to become more involved with decisions about treatment*

Drugs for psychiatric problems are prescribed on the assumption that they mostly act against neurochemical substrates of disorders or symptoms. In this article we question that assumption, proposing that drugs' action be viewed rather as producing altered, drug induced states, a view we have called the drug centred model of action. We believe that this view accords better with the available evidence. It may also allow patients to exercise more control over decisions about the value of pharmacotherapy, helping to move mental health treatment in a more collaborative direction.

#### Assumptions about mode of action

The widespread use of psychiatric drugs is justified by the idea that they work by correcting, or helping to correct, underlying biological abnormalities that produce particular psychiatric symptoms. We have called this view the disease centred model of psychiatric drug action (table 1). Most drugs used in medicine can be understood as working according to a disease centred model—even analgesics, for example, work by acting on the physiological mechanisms that produce pain. In psychiatry, the disease centred model is reflected in the names of the major drug classes: antidepressants are believed to reverse biochemical pathways that give rise to symptoms of depression and antipsychotics are thought to act on mechanisms that produce psychotic symptoms. From this viewpoint, the therapeutic actions of drugs (their actions on disease processes) can be distinguished from other effects, accordingly termed side effects.

**View this table:** Models of psychiatric drug action

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An alternative, drug centred model of drug action, stresses that psychiatric drugs are, first and foremost, psychoactive drugs. They induce complex, varied, often unpredictable physical and mental states that patients typically experience as global, rather than distinct therapeutic effects and side effects (table 2). Drugs may be useful because some altered states can suppress the manifestations of certain mental disorders.

The disease centred model of drug action developed in the 1950s and 1960s and replaced a drug centred understanding of how psychiatric drugs worked.<sup>1</sup> For example, the early investigators of neuroleptic or antipsychotic drugs suggested that they worked by

inducing a neurological syndrome consisting of physical restriction and mental symptoms such as cognitive slowing, apathy, and emotional flattening, which resembled Parkinson's disease.<sup>2</sup> These effects also reduced the intensity of psychotic symptoms. Thus, extrapyramidal effects, and their conjoined mental effects, were not regarded as side effects but as the mechanism by which the drugs produced their intended outcome.<sup>3</sup>

Inducing overt parkinsonism has long been thought unnecessary to produce a therapeutic effect, yet there has been little consideration of the mental alterations produced by neuroleptic drugs and just how these might interact with psychotic symptoms. Some modern commentators have suggested that the emotional indifference induced by neuroleptics accounts for their therapeutic effects,<sup>4</sup> and empirical research supports this position.<sup>5</sup> Overall, the drug centred model suggests looking more closely at how psychological alterations produced by psychiatric drugs interact with the experiences of distress and psychosocial disability that lead people to seek clinical help.<sup>6</sup>

## Evidence on psychiatric drug action

Both models help clarify possible mechanisms of drug action and need not be mutually exclusive. However, the neglect of the psychoactive effects of psychiatric drugs has made it difficult to establish disease specific actions. For example, placebo controlled trials are not designed to distinguish whether observed outcomes occur because of the drug's action on an underlying pathological process or as a consequence of being in an altered state. Psychoactive effects, including sedation, psychomotor slowing, activation, and altered sense perception, could have an effect on the symptoms of distress in countless disorders and be distinguished from effects associated with inert placebo.<sup>6</sup> Any drug with sedative properties, for example, will modify disturbances of sleep and arousal found in many psychiatric conditions and in the disorder specific rating scales used in clinical trials.

A second difficulty has been a paucity of realistic trials that use active placebos or compare drugs believed to be disorder specific (according to current diagnostic classifications or theories) with other drugs known to exert some psychoactive effects. Early trials comparing chlorpromazine and barbiturates favoured chlorpromazine, but comparisons with benzodiazepines give mixed results,<sup>7</sup> and a trial using opium as a comparator found no difference.<sup>8</sup> However, although evidence of the superiority of antipsychotics might imply disease specific effects, superior effects can also be explained within a drug centred framework. This view suggests that the characteristic psychomotor and emotional restriction induced by antipsychotics is more effective at suppressing psychotic agitation than other sedatives, as proposed by the early investigators.<sup>2</sup>

Drugs not normally considered to be antidepressants, including antipsychotics, benzodiazepines, and stimulants, have been found to have comparable effects to antidepressants in people with depression.<sup>9</sup> Comparisons of lithium with antipsychotics and benzodiazepines have not confirmed its superiority to treat mania or affective psychosis.<sup>10</sup> Although one study suggested some differential effect on particular symptoms,<sup>11</sup> others have not.<sup>12</sup>

Biochemical aetiological theories such as the dopamine theory of schizophrenia or psychosis and the monoamine hypothesis of depression seem to support a disease centred view of drug action, although their strongest support remains the presumed specificity of drug treatment. Proponents of the dopamine hypothesis argue that antipsychotics exert their therapeutic action by correcting an underlying dopamine dysregulation.<sup>13</sup> However, little evidence suggests that any abnormality of the dopamine system is specific to psychosis and not accounted for by other factors associated with dopamine activity, such as increased arousal or stress. That some effective antipsychotic drugs such as clozapine have relatively weak actions on dopamine receptors also seems to contradict the theory.<sup>14</sup>

Evidence for the monoamine hypothesis, which states that antidepressants work by countering a deficiency of noradrenaline or serotonin activity, is also questionable. Many different investigations of the drugs' metabolites and receptors in depressed people and postmortem examinations have produced no reliable demonstration of such a deficiency.<sup>15</sup>

Generally, there have been few attempts to evaluate the dominant, disease centred explanation for drug action in psychiatry because few people realise that an alternative explanation exists.<sup>1</sup> The little available evidence does not yet provide compelling grounds to accept the disease centred model.

## Drug centred model in research

There has been little systematic exploration of the full range of psychoactive and physical effects produced by psychiatric drugs. This information is typically obscured by short clinical trials that focus on narrow complaints and outcomes and relegate other effects to the status of side effects.<sup>16</sup> There is also a paucity of research on the often unpredictable, long term effects of drugs, the consequences of drug withdrawal, and the nature of the large black box presently called the placebo effect.

For example, the nature of the subjective state induced by taking selective serotonin reuptake inhibitors (SSRIs), and how it interacts with expectancy effects, remains unclear. Volunteer studies suggest these drugs may have concurrent sedative and activating or stimulant effects,<sup>17</sup> and some research indicates they reduce emotional responsiveness, but this has not been

confirmed.<sup>18</sup> How they cause suicidal ideation, if they do, is also not established. Similarly, few data exist about the subjective effects produced by second generation antipsychotics, how they differ from each other, and whether they are similar to the effects produced by older antipsychotics. Obviously, this information is crucial if people are to make informed choices about whether these drugs are likely to improve their mental state and what price might be paid in return.

More comprehensive volunteer studies are needed to obtain data on the full range of effects of psychiatric drugs. It is also important to pay attention to patients' uncensored accounts of taking psychiatric drugs, available on the internet, for example. Clinical trials need to devise ways to explore patients' experiences more directly than through clinicians' diagnoses and symptom rating scales. Patients' views also need to be collected after the drugs have been stopped, since many effects may be difficult to identify while in a drug induced state.

## Implications for clinical practice

Messages conveyed in information leaflets and advertising campaigns have persuaded millions of people that mental disorders are caused by chemical imbalances that can be rectified by drugs.<sup>19</sup> However, given the paucity of the evidence, we suggest that prescribers should not present the drugs they prescribe for mental disorders as disease specific treatments. Psychiatric drugs might need renaming, to avoid the presumption of specificity built into labels like antidepressants and antipsychotics.

The drug centred model may change attitudes to psychiatric drugs and empower patients to be more involved in decisions about treatment. Whereas a disease centred model has a built-in assumption that drug treatment is likely to be physiologically corrective and therefore beneficial, a drug centred model, by stressing that drugs are extrinsic substances that alter how the body works, demands that the advantages and disadvantages of taking a drug be carefully weighed up and distinguished from the effects of treatment in general. Highlighting that psychiatric drugs are psychoactive substances allows people to judge for themselves what sort of drug induced effects might help them and what sort might not. Patients become the ultimate arbiters of the value of taking a particular drug and are encouraged to take an active role in adjusting drug regimens to suit their needs.

In the short term, for example, the cognitive and emotional suppression described by people who have taken antipsychotic drugs may bring relief to someone traumatised by intense psychotic experiences and allow people to engage better with the world around them.<sup>20</sup> However, after recovery from an acute episode, some people may decide that the costs of continued drug treatment are not outweighed by the reduction in the risk of relapse that long term treatment may produce. According to a drug centred model, therefore, non-compliance may be a rational response to the effects of drugs, which prescribers need to understand and accommodate rather than overcome.

People with depression are likely to respond differently to an offer of a drug intended to produce an altered state than a drug said to act on the underlying biological mechanism of depressive symptoms. Various psychoactive drugs, such as antipsychotics and possibly SSRIs, may suppress the experience or expression of emotions, including feelings of depression, but it seems unlikely that many people would desire this kind of effect. On the other hand, some people with depression may find drugs with sedative effects, such as benzodiazepines and low dose tricyclic antidepressants, useful temporarily to bring relief from troubled sleep, anxiety, and agitation.

In this way, the drug centred model provides a rationale for periodic rather than continuous drug use, to cope with exacerbations of symptoms or to palliate stressful environmental events and avoid the harm associated with long term use. It questions the use of complex drug cocktails, commonly prescribed in the United States, for example, based on the presumed fit between different drugs and multiple diagnoses given to a patient. It also allows doctors, patients, and people who know patients to properly monitor the full consequences of drug treatment and engage in an ongoing dialogue about how it compares with alternative interventions.

Medicine, as a whole, has started to recognise the importance of involving patients in decisions about their care. By highlighting the nature of psychiatric drugs as psychoactive substances that produce altered states, the drug centred model may enable patients to participate more equally in the process of evaluating the likely effect of drug treatment in their particular situation. A drug centred model also imposes a duty on the psychiatric research community to produce relevant, unbiased information about the range of effects that psychiatric drugs exert on thought, emotion, and all bodily systems, both during short term and long term use. At present, the influence of the disease centred model keeps the full range of effects of many drugs obscured, and hence neither doctors nor patients can make properly informed decisions about the risks and benefits of using them.

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