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Rethinking Models of Psychotropic Drug Action

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Abstract
Theoretical assumptions about how psychotropic drugs 'work' are rarely discussed explicitly. In a 'disease-centred model,' drugs are believed to work by acting on a disease process. In contrast, in a 'drug-centred model,' the characteristic physiological, behavioural and subjective effects of drugs are used to define drug action. The therapeutic value of a drug stems from the usefulness of these effects in clinical situations. The disease-centred model appears dominant but has weaknesses: (1) it cannot logically justify the use of drugs since major pathophysiological hypotheses were derived from selectively observed actions of drugs; (2) comparisons between drugs believed to have specific effects in certain conditions and drugs thought to have non-specific effects fail to support it; (3) outcome measures for various disorders include items responsive to non-specific drug effects; (4) studies with healthy volunteers describe characteristic drug-induced states independently of a psychiatric diagnosis; (5) animal tests show effects with agents not usually thought of as specific treatments for the conditions modelled by tests. This article offers suggestions to develop a drug-centred model and discusses its potential impact on clinical practice.

Modern psychopharmacology, or the study, classification and clinical use of psychotropic drugs, developed in the 1950s alongside the introduction of new drug treatments in psychiatry. However, in contrast to numerous empirical descriptions of drug effects on aspects of psychopathology, there are few discussions of theoretical assumptions about drug action. Such assumptions nonetheless exist and influence the treatment of mental disorders. Indeed, psychiatric drug treatment is currently predicated on a 'disease-centred' model of drug action, which proposes that most psychiatric drugs act as specific treatments for specific conditions. Current nomenclature embodies this position with names like antipsychotics, antidepressants, anxiolytics, antimanics and mood stabilisers. Models describe general principles to help achieve a deeper understanding of natural and social processes. Models guide scientific inquiry and produce therapeutic advances that may, in turn, lead to the development of more complex models. In this article we outline the disease-centred model of drug action and critically evaluate the different lines of evidence that support it. We also describe an alternative, 'drug-centred' approach and some of its treatment implications.

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Models of Drug Action in Psychiatric Disorders

The Disease-Centred Model

The disease-centred model underlies orthodox psychopharmacology. Its core assumption is that psychotropic drugs help to correct a biochemical abnormality that represents a biological substrate of a specific disease process. This notion, borrowed from certain paradigmatic treatments such as the use of insulin in insulin-dependent diabetes, is sometimes called the 'chemical imbalance' theory of mental disorders. Although this model is rarely explicated nowadays, its influence can be inferred from the classification of psychotropic drugs according to the disorders they are believed to treat. In turn, efficacy trials and animal research are principally organized around this classification. In clinical practice, the disease-centred model is often presented to patients as the basis for their need to take medication, with many psychiatrists drawing analogies between mental disorders and diabetes or hypertension, for example. Some patient information, published by professional bodies and pharmaceutical firms, states explicitly that drugs work by correcting biochemical abnormalities [1, 2, pp. 181–182].

A variant of this model is the symptom-centred model. Here, drugs are believed to act on the pathological processes producing the symptoms rather than on the underlying disease process. For example, antipsychotic drugs are hypothesized to disrupt the production of psychotic symptoms by blocking dopamine over-activity [3]. This might be analogized by the action of analgesics such as opiates, that reduce and inhibit transmission of nociceptive stimuli along spino-thalamic pathways, or non-steroidal anti-inflammatory drugs, that inhibit the production of prostaglandins involved in producing pain that arises from inflammatory reactions [4]. Although this model appears more pragmatic, it still rests on notions that drugs work by affecting specific abnormal biochemical or neurophysiological processes that give rise to symptoms.

In a rare recent discussion of the theoretics of psychotropic drug action, Hyman and Nestler [5, 6] reject the emphasis on synaptic neurotransmitters as the basis of understanding drug action, proposing instead that therapeutic effects result from impacts on neural circuits. Although these authors attempt to address some problems of conventional views of drug action, their ideas remain grounded in a disease-centred model that assumes that 'pharmacotherapeutic agents produce their clinically beneficial effects in an abnormal nervous system' and that these effects 'counter or compensate for the abnormal pathophysiology' [6, p. 440].

The Drug-Centred Model

The disease-centred model of drug action is rejected or seen as limited by critics, practitioners and scholars of psychopharmacology [2, 7–11]. Common threads in their arguments include: (a) the high degree of integration of the central nervous system, such that even drugs with specific targets necessarily produce non-specific actions, (b) the lack of validation of a disease model of psychopathology and (c) the clinical use of similar drugs for different disorders and the use of pharmacologically dissimilar drugs for similar disorders. Existing critiques converge to suggest that the evidence on psychotropic drug effects points to the validity of a 'drug-centred' model.

In this approach, drugs are seen to induce characteristic physiological and subjective states that may, or may not, be experienced as useful in certain social and interpersonal situations, including clinical situations. Unlike the disease-centred model that assumes that drugs move an abnormal physiological state towards a more normal one, the drug-centred model suggests that drugs create their own characteristic abnormal states or alterations of normal states. It is these states or effects that need to be described and understood, and the potential therapeutic value of a drug is deduced from this understanding. It is therefore implied that diagnosed patients and normal volunteers' basic physiological responses to drugs will differ only insofar as a degree of individual variation in drug response (including variation in arousal, set, biological sensitivity) always exists.

Historically, an elementary drug-centred classification of drug action distinguished drugs on the basis of primarily sedative (or 'depressant') and stimulant effects. A more elaborate classification might distinguish between different types of sedative effects of conventional antipsychotics, tricyclic antidepressants, benzodiazepines, barbiturates and opiates and could start to characterize the sedation from the newer antipsychotics. Similarly, stimulating effects of 'classic' psychostimulants, some types of 'antidepressants', and other drugs could be differentiated more finely. Such a classification would also need to consider drugs that cause sedation and agitation simultaneously, such as some antipsychotics and antidepressants. Other effects, including psychomotor indifference, akinesia, akathisia, hallucinogenesis, euphoria and dysphoria, require further elaboration and suggest yet more ways to characterize drug actions.

The case of alcohol briefly illustrates the implications of the model. Alcohol reduces conductivity in the central nervous system. Ingestion of alcohol gives rise to characteristic physiological effects, such as vasodilation and slowed reaction times, and to various characteristic subjective experiences and behavioural effects such as euphoria, social disinhibition and sedation. These effects – usually dose dependent – have several consequences. They are responsible for the popularity of alcohol as a social lubricant and recreational substance; they can lead to aggressive and reckless behaviour in some circumstances; they can produce withdrawal syndromes after prolonged use at high doses, and they may help people to overcome some behavioural inhibitions. Alcohol might therefore be seen as a possible treatment for 'social phobia', not because the substance corrects an underlying physical abnormality in social phobia, but because one type of effect produced by alcohol might in itself be useful for people experiencing difficulties in some interpersonal or social situations. In this connection, dramatic beneficial effects of ethyl alcohol on patients with schizophrenia have been described [12, p. 287; 13].

Other examples of drug-centred thinking were provided by early proponents of modern psychopharmacology. Pierre Deniker, credited with the first major psychiatric use of chlorpromazine, thought that its useful effects were attributable to the induction of an abnormal encephalitis-like state characterized by 'psychomotor indifference' [14, p. 92]. Others described chlorpromazine's particular advantages as its ability to produce 'a calming effect with a minimum of drowsiness and confusion' [15, p. 540], or a 'pathological tranquillity of mind' [16, p. 961].

Development of the Disease-Centred Model

Prior to the 1950s, a 'drug-centred' pragmatic model guided the use of drugs in psychiatric practice, although other theoretical frameworks were sometimes proposed. Drugs were classified crudely into sedatives and stimulants, as exemplified by Sargant and Slater's [17] discussion of 'chemical sedation and stimulation' in their 1944 textbook of physical treatments in psychiatry. These authors recommended sedative drugs to induce sleep and to calm acutely agitated patients. Sargant and Slater specifically recommended prescribing phenobarbitone as a 'basic sedative and not *pro re nata*' [p. 87; italics in original translate as 'for the thing of origin']. Sargant and Slater did not generally find stimulants useful in psychiatric conditions, because stimulant and euphoric effects rapidly diminished with continuing use. However, these authors did consider stimulants to be useful in children with electro-encephalographic abnormalities and hyperactivity, in which symptoms 'may yield to the drug in what appears a specific way' [p. 96]. Apart from the latter example, however, drugs were not seen as exerting effects on the underlying condition being treated. For this, treatments such as electroconvulsive therapy or insulin coma were seen as necessary. In 1954, an influential English textbook of psychiatry by Mayer-Gross et al. [18] stated that 'hypoglycaemic treatment clearly touches the physical basis of schizophrenia more closely than all earlier modes of attack' [p. 286]. This was one of many expressions of a desire for a specific therapy in psychiatry before the modern drug treatment era [13, 19].

In contrast to earlier ideas about drugs, views that emerged from the 1950s onwards fairly rapidly came to characterize drugs as having specific effects in different conditions, and drugs began to be classified basically according to the condition for which they were felt to be effective [19]. Recent histories of psychiatry and psychopharmacology [8, 20, 21] suggest numerous factors that may have reinforced the adoption of a disease-centred model of drug action. These factors include: the desire to develop psychiatric treatments with similar specificity as some other medical treatments; the neo-Kraepelinian trend toward viewing disorders as discrete entities with specific aetiologies [22]; the development of molecular biological tools and the resulting focus on synaptic hypotheses of drug action; requirements of drug licensing bodies [9], and the penetration of psychiatric thinking by the marketing language used by pharmaceutical companies [2].

However, the historical evidence suggests that the specificity of the new drug treatments was assumed or asserted before authors discussed what it might mean for a drug to be specific for a particular psychiatric condition, and what sort of evidence might be needed to reach this conclusion. Although the assumption that psychiatric drugs are specific still underlies most research in clinical psychopharmacology and most professional and popular discourse, the case that psychiatric drugs are specific either to diseases or to pathological processes is far from established. In the following section, it is argued that much of the evidence that would be needed to justify this position is lacking, and the evidence thought to support it is often inadequate.

Deficiencies of the Disease-Centred Model

Derivation of Disease Models from Observations of Drug Effects

The major justification for a disease-centred model of a drug's action is if the pathophysiology of the disease is described independently of, and usually prior to, the use of the drug treatment. Within this framework, an effective drug – such as insulin for diabetes or penicillin for a bacterial infection – is one that affects a part of this pathophysiology. However, modern pathophysiological hypotheses in psychiatry either derive largely from the known or presumed mechanisms of actions of drugs used to treat the conditions, or have been adapted to accommodate drug action. The most famous, the dopamine hypothesis of schizophrenia, arose directly from the elucidation of some pharmacological effects of the first antipsychotic drugs [23]. Subsequent refinements, such as speculation about the role of serotonin in psychosis, resulted from using antipsychotics with actions on a seemingly greater number of neurotransmitter systems including serotonin. The monoamine hypothesis of depression was also elaborated in conjunction with research on the actions of antidepressants [8]. Hypotheses about the neurobiological basis of anxiety also derive from observations of benzodiazepines' effects on the gamma-aminobutyric acid receptor complex [24], while the clinical use of selective serotonin reuptake inhibitors has increased theorizing on the role of serotonin in anxiety [25]. Most ideas about the physiological and biochemical underpinnings of psychiatric conditions therefore *assume*, rather than provide compelling support for, the disease-centred model of drug action.

Research attempting to find independent evidence of the suggested biochemical abnormalities has not, to date, produced conclusive findings in any mental disorder. Some recent imaging studies, showing increased levels of dopamine activity in acute psychosis [26], have led to a renewed interest in the dopamine-psychosis relationship [3]. However, the evidence is inconsistent, and it remains unclear whether abnormalities of dopamine activity are specific to schizophrenia or psychosis, or merely features of an altered state of arousal or some other aspect of an acute psychiatric condition.

Basing a model of drug action on the observed efficacy of drugs used to treat a given psychiatric condition raises two further problems. The first is that 'efficacy' in psychiatric disorders is a historically and even geographically relative construct. What it means for a psychotropic drug to be considered 'efficacious' is subject to periodic revision based on changing nosological systems, drug regulatory requirements, clinical trial methodologies and definitions of relapse. Some medical treatments such as insulin for diabetes and antibiotics incontrovertibly return functioning to normal or near normal. The effects of psychiatric treatments are more subtle, and desirable effects under one era's standards may not be valued in another era. Secondly, observations or inferences about drugs' modes of action are usually selective. Thus, biochemical hypotheses of depression focus on the synthesis, release, metabolism and/or receptor sites of one or two members of a single neurotransmitter family, whereas antidepressants influence almost all neurotransmitters, most hormones and many neuropeptides [27]. Further, the initial sites of action of a drug, where pharmacological activity is more easily measured, are part of a long-lasting chain of adaptive events that usually overwhelm a drug's early activity [5].

Failure to Establish Clear Differences with Non-Specific Drugs

Demonstrating that drugs believed to be specific have superior, or at least different, clinical effects than drugs with non-specific actions would seem to be a prerequisite to establish specificity of action. Surprisingly, such studies are rare and most were conducted decades ago. For example, evidence suggesting that antipsychotics are superior to other sedatives in the treatment of psychosis is sparse and inconsistent. Two early trials found that various phenothiazines were superior to phenobarbital in patients with acute and chronic schizophrenia [28, 29]. However, a trial comparing opium and chlorpromazine produced equivalent improvement over 3 weeks in acute schizophrenia [30]. Wolkowitz and Pickar [31] found 13 double-blind trials comparing benzodiazepines with placebo and/or neuroleptics. Six studies compared a benzodiazepine and placebo for patients with acute and chronic psychotic diagnoses; only the largest study found the benzodiazepine to be markedly superior to placebo at a statistically significant level. However, in the 6 trials comparing benzodiazepines with neuroleptics, the outcomes were equivalent in 3, the benzodiazepine was superior in 2, chlorpromazine was superior in 1, and in 1 trial the benzodiazepine was equivalent to haloperidol but inferior to chlorpromazine. In 7 of the 10 studies where psychotic symptoms were measured separately, benzodiazepines reduced symptoms comparably to neuroleptics or better than placebo. Comparable effectiveness between benzodiazepines and neuroleptics was recently observed in treating exacerbation signs in schizophrenia [32].

Numerous studies of the treatment of depression compare agents not primarily regarded as antidepressants with either placebo or standard antidepressants [33]. Several antipsychotics, some benzodiazepines, barbiturates, opioids and stimulants as well as buprenorphine and buspirone, have shown superiority to placebo or equivalency to antidepressants. However, given the deeply ingrained assumption that antidepressants are specific treatments for depression, such findings are usually explained by suggestions that these other agents may have 'antidepressant properties' [34]. One alternative explanation suggests that antidepressants have non-specific effects. They may work by causing sedation, which reduces agitation associated with depression, induces sleep and may mask depressive feelings. Antidepressants may also work by enhancing the placebo effect, as when physiological reactions to a drug reveal or confirm to patients that they are taking an active medication [35]. In this case, almost anything might turn out to have antidepressant properties, and the literature indeed suggests this might be so.

Lithium has long been designated as a specific treatment for bipolar disorder. However, studies of treatment of acute mania have not shown that lithium is superior to neuroleptics, and it has been found to be inferior for the treatment of highly overactive patients [36, 37]. In addition, studies comparing patients with manic, schizoaffective and schizophrenic psychoses have not shown that lithium differs from antipsychotics in its effects in different diagnostic groups [38, 39]. The specificity of lithium as a prophylactic treatment has also not been established, since careful comparisons with other drugs with strong sedative effects, excepting anticonvulsants, have not been done. In addition, although the efficacy of lithium as a prophylactic treatment is generally accepted, concerns have been raised about the methodological validity of the placebo-controlled trials that established this [40]. In particular, evidence that lithium withdrawal increases risk of relapse over and above the untreated risk [41, 42] suggests that the results of these trials may have been confounded by lithium withdrawal effects. Although the reality of a lithium withdrawal phenomena is not universally accepted [43], recent data provide further evidence for its existence [44].

Inclusion of Non-Specific Items in Drug Rating Scales

Common scales used for rating outcomes in psychopharmacology trials contain items describing behaviour that would not normally be considered a specific part of the disorder being treated and would be expected to respond to non-specific effects of medication. For example, the 17-item Hamilton Rating Scale for Depression contains 7 items on sleep disruption and anxiety, all of which can be expected to respond to sedative effects of drugs. Psychosis rating scales also contain items that relate to arousal and would also respond to sedative effects nonspecifically. The Brief Psychiatric Rating Scale contains items on tension, uncooperativeness, excitement and hostility. Similarly, of 7 items on positive symptoms in the Positive and Negative Symptom Scale, 2 items concern excitement and hostility. In drug efficacy studies employing such instruments that partly rate non-specific effects, changes in the global scores do not necessarily signify that a drug has a specific effect on a particular disorder.

Similar Effects in Diagnosed Patients and Healthy Volunteers

The disease-centred model suggests that drugs are likely to have different effects in people with the condition for which the drugs are indicated compared with people without the condition [6]. However, surprisingly few studies describe the subjective and behavioural effects of psychotropic drugs on human volunteers or patients with other conditions, and effects seen in volunteers are usually dismissed as side effects. For antipsychotic drugs, available studies show unambiguous drug effects consisting of impaired performance on psychomotor and cognitive tasks [45–47] and subjective effects, including sedation, dysphoria, akathisia, and feelings variously described as disengagement, indifference or depersonalization [45, 48]. These effects are consistent with effects seen in patients and usually described as side effects. However, it is also apparent that these same effects might be responsible for reducing agitation and psychotic symptoms [49].

Effects of lithium in volunteers include slowing of performance on cognitive tasks, tiredness, lethargy, dysphoria and occasionally confusion [50, 51] – experiences consistent with electroencephalogram changes showing increased slow wave activity [52]. This pattern of effects could explain lithium's action in acute mania.

The few available studies of antidepressants in volunteers suggest that different antidepressants show different effects. This is consistent with the fact that antidepressants come from a variety of different pharmacological classes. For example, in one study reboxetine appeared to be mildly stimulant and sertraline to be mildly sedating [53]. Amitripyline has been found to be profoundly sedating and cause cognitive impairment and electroencephalographic changes similar to those of chlorproma-

zine [54]. Effects on affect and mood in volunteers have rarely been demonstrated and are not clear cut. Conventionally, this is taken as evidence that antidepressant effects are only apparent in depressed patients. However, a recent meta-analysis found that overall therapeutic effects in patients – as measured by the Hamilton Rating Scale for Depression – were also small, and could easily have been achieved by non-specific effects such as sedation [55]. The current confusion and lack of information about the physiological, behavioural and subjective effects of most antidepressants illustrates a limitation of the disease-centred model.

Limitations of Animal Screening Research

Numerous animal screening tests are meant to identify compounds that might have specific effects on psychiatric disorders by using animal assay or homologous models of these disorders [56]. The limitations of animal models in use are widely acknowledged [57], but it is rarely pointed out that they often fail to discriminate between supposedly specific drugs and non-specific ones. For example, in all animal models of depression, responses are obtained with drugs that are not generally considered to have antidepressant activity in humans [58]. In the forced swim test, one of many tests used to screen for antidepressants, positive results have been obtained with amphetamines, opiates, antihistamines, some antipsychotics, atropine, pentobarbital as well as zinc and antibiotics [58, 59]. In line with the underlying assumption that 'antidepressant activity' can be specifically identified or isolated, some authors label these results as 'false-positives' [58]. Conversely, the selective serotonin reuptake inhibitors, widely considered to be specific antidepressants, typically fail to be detected by the forced swim test [60].

Developing a Drug-Centred Model of Drug Action

Jacobs and Cohen [61] have pointed out how little is known about the 'psychological alterations' produced by psychotropic drugs. These authors described the limitations of the randomized controlled trial for evaluating the full range of a drug's effects and the spurious nature of the distinction between therapeutic and adverse effects. Other authors have also criticized various aspects of current methodology [62, 63] and some have emphasized the importance of finding new methods to explore 'treatment-specific efficacy' [64]. The drug-centred model outlined here suggests a programme for developing a fuller understanding of the effects of psychotropic drugs which could include the following features:

- *A priority on detailed investigations of what different types of drug-induced experiences consist of.* This would involve more studies with volunteers and patients – over durations more closely approximating actual clinical treatment – that focus on the nature of the subjective experience as well as physiological and behavioural measures of 'drug response'.
- *Developing outcome measures addressing particular behaviours rather than disorders.* Use of outcome measures designed to measure disorders should be replaced by measures that address particular behaviours that patients or others desire to be modified.
- *Constructing a new vocabulary of drug-induced effects.* For example, different types of sedative, stimulant and other drug-induced effects could be characterized. Such a vocabulary could provide the basis to group drugs according to similarities in the effects they produce.
- *Integrating the literature on adverse effects with that on therapeutic effects.* According to a drug-centred model of drug action, the distinction between therapeutic effects and adverse effects is arbitrary. Research under such a model would aim to obtain a complete picture of the range of a psychotropic drug's action.
- *Investigating in more detail the potential benefits of using non-specific drugs that are better tolerated by patients, such as benzodiazepines, as the main treatment for acute psychiatric syndromes.* This would include comparisons with standard psychiatric drug treatments.
- *Evaluating patients' comparative preferences for different types of drugs in various situations.*
- *Obtaining patients' post-treatment ratings of drug effects.* The evaluation of a psychotropic drug may be considered incomplete until the user has had a chance to look back on the drug-taking experience from a drug-free standpoint.

Implications of a Drug-Centred Model for Psychiatric Practice

Clinical practice suggests that a drug-centred approach to psychiatric drug treatment may not have been totally abandoned with the psychopharmacological revolution of the 1950s. Psychotropic drug handbooks list numerous different classes of drugs as appropriate for a given condition. Nearly every single class of psychotropics, for ex-

ample, has some indication for the treatment of psychosis [65]. Benzodiazepines are widely used to treat acute and chronic psychosis and other behavioural disturbances [66]. Clinicians may thus appear to practise something of a drug-centred approach while alleging a disease-centred rationale for prescribing. However, on its own terms, the drug-centred approach appears to deserve more serious engagement by practitioners and researchers.

A drug-centred model would require a transformation in clinicians' explicit approach to the management of psychiatric conditions. For example, sedation or tranquilization could become an explicit (short-term) treatment strategy, not merely in emergency situations, but for the duration of acute psychotic episodes or situations where someone was experiencing severe agitation. This approach need not induce pessimism about possibilities for clinical improvement. As understood by many psychiatrists treating schizophrenic patients in the 1950s and 1960s, the tranquilization theory supposed that patients hallucinated less, were less tense, or manifested less pressured speech precisely *because* they were tranquilized [20, pp. 68–69]. Sedation does not preclude diverse effects on symptoms, simply a less specific method of short-term pharmacological action.

Psychiatric treatment based on a drug-centred model of drug action has the potential to be a more democratic and user-oriented activity than it currently is. It involves determining whether the effects of different drugs have utility to lessen the distress associated with various dysfunctional emotional and behavioural states. This requires an equitable dialogue between psychiatric service users and professionals, with both parties sharing their different knowledge and perceptions of drugs' action and potential utility [67, 68]. However, for consensual psychiatry, it is ultimately the user's experience that determines a drug's utility and value.

A psychiatry that squarely incorporated the drug-centred model would focus strongly on the balance between the pros and cons of using drugs in different situations. What this would mean in practice will require substantial elaboration, but can be illustrated by considering the management of acute psychosis and depression. The induction of sedation, indifference and akinesia by antipsychotic drugs may be perceived as useful in acute psychosis, by patients or by others. However, in the long-term, such effects are unlikely to be conducive to a return to normal functioning. In addition, the reality that taking most antipsychotic drugs is so often an aversive experience means that even if these drugs appear uniquely useful at suppressing acute psychotic symptoms, people might opt for other sorts of treatments given the choice. In the management of depression, some people may find sedative drugs or stimulants useful in the short term. However, these strategies need to be set against possible negative effects, such as hindering or delaying the process of self-directed recovery.

It remains to be determined whether a drug-centred model of drug action, by providing a more balanced view of the benefits of drug treatment but also by creating new ways to promote drug usages, would lead to a reduction or an increase in the use of prescribed psychotropic drugs. Whatever the outcome, it would demand that mental health professionals become better informed about the nature of effects of different psychotropic drugs in order to enter into a constructive dialogue about their genuine utility with consumers. Similarly, it would require the development of new directions for psychopharmacology research, much of which would also need to be conducted in collaboration with consumers. In view of the limitations of the disease-centred model outlined in this paper, a drug-centred approach deserves further exploration and elaboration.

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