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Commentary

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Why are doctors still prescribing neuroleptics?

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Summary

There are two main pharmacological methods of suppressing undesired behaviour: sedation or neuroleptics. Traditionally, the invention of neuroleptics has been hailed as one of the major clinical breakthroughs of the twentieth century, since they calmed agitation without (necessarily) causing sedation. The specifically neuroleptic form of behavioural control is achieved by making patients psychologically Parkinsonian, which entails emotional blunting and consequent demotivation. Furthermore, chronic neuroleptic usage creates dependence, so that in the long term, neuroleptics are doing most patients more harm than good. The introduction of 'atypical' neuroleptics (neuroleptically-weak but strongly sedative neuroleptics) has made only a difference in degree, and at the cost of a wide range of potentially fatal metabolic and other side-effects. For half a century, the creation of millions of Parkinsonian patients may have been misinterpreted as a 'cure' for schizophrenia. Such a wholesale re-interpretation of neuroleptic therapy represents an unprecedented disaster for the self-image and public reputation of both psychiatry and the whole medical profession. Nonetheless, except as a last resort, neuroleptics should swiftly be replaced by gentler and safer sedatives.

Introduction

It is usually said, and I have said it myself, that the invention of neuroleptics was one of the major therapeutic breakthroughs of the twentieth century.[1] But I now believe that this opinion is due for revision, indeed reversal. Neuroleptics have achieved their powerful therapeutic effects at too great a cost, and a cost which is intrinsic to their effect.[2,3] The cost has been many millions of formerly-psychotic patients who are socially docile but emotionally blunted, demotivated, chronically neuroleptic-dependent, and suffering significantly increased mortality rates. Consequently, as a matter of some urgency, neuroleptic prescriptions should be curtailed to the point that they are used only as a last resort.

Behavioural suppression in medicine

Psychiatrists, especially those working in hospitals, have frequent need for interventions to calm and control behaviour: either for the safety of the patient or that of society. The same applies, less frequently, for other medical personnel dealing with agitation, for example due to delirium or dementia. Broadly speaking, there are two pharmacological methods of suppressing agitated behaviour: sedatives or neuroleptics.[2,3]

Sedation was the standard method of calming and controlling psychiatric patients for many decades prior to the discovery of neuroleptics, and sedation remained the only method in situations where neuroleptics were not available (e.g. in the Eastern Bloc and in developing countries).[3,4]

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The therapeutic benefits of sedation should not be underestimated. Sedation can usually be achieved safely and without sinister side-effects, and improved quality of sleep often makes patients feel and function better. Sedation may also be potentially 'curative' where sleep disturbance has been so severe and prolonged as to lead to delirium, which (arguably) may be the case for some psychotic patients, such as those with mania.[2,5]

But clearly (except in the short term) sedation is far from an ideal method of suppressing agitation. The discovery of neuroleptics offered something qualitatively new in terms of behavioural control: the possibility of powerfully calming a patient without (necessarily) making them sleepy.[4] In practice, sedative neuroleptics (such as chlorpromazine or thioridazine), or a combination of a sedative (such as lorazepam or promethazine) with a less-sedating neuroleptic such as haloperidol or droperidol, were often used to combine both forms of behavioural suppression.

But neuroleptics have four big problems. The first is that the core 'therapeutic' and behaviour-controlling effect of neuroleptics is to induce Parkinsonism.[2,4,6] The second problem is that neuroleptics (like many or most psychoactive agents) create dependence when used in the long term, and it may become almost impossible to withdraw from them without provoking a psychotic breakdown.[6,7] The third problem is that they are neurotoxic, and can cause a form of permanent Parkinsonism even after total withdrawal (the syndrome termed tardive dyskinesia, which may, or may not, be relatively less problematic with the 'atypicals').[4,6,8] And the fourth major problem is that neuroleptics are exceptionally dysphoric[9]—most people find them extremely unpleasant to take, and consequently a huge coercive apparatus (including long-acting injectable formulations) has been created to ensure compliance.[6]

The Parkinsonian core effect of neuroleptics

The Parkinsonian (emotion-blunting and de-motivating) core effect of neuroleptics has been missed by most observers. This failure relates to a blind-spot concerning the nature of Parkinsonism.

Parkinsonism is not just a motor disorder. Although abnormal movements (and an inability to move) are its most obvious feature, Parkinsonism is also a profoundly 'psychiatric' illness in the sense that emotional blunting and consequent demotivation are major subjective aspects. All this is exquisitely described in Oliver Sack's famous book *Awakenings*,[10] as well as being clinically apparent to the empathic observer.

Emotional blunting is demotivating because drive comes from the ability subjectively to experience in the here-and-now the anticipated pleasure deriving from cognitively-modelled future accomplishments.[2] An emotionally-blunted individual therefore lacks current emotional rewards for planned future activity, including future social interactions, hence 'cannot be bothered'.

Demotivation is therefore simply the undesired other side of the coin from the desired therapeutic effect of neuroleptics. Neuroleptic 'tranquillization' is precisely this state of indifference.[8] The 'therapeutic' effect of neuroleptics derives from indifference towards negative stimuli, such as fear-inducing mental contents (such as delusions or hallucinations); while anhedonia and lack of drive are predictable consequences of exactly this same state of indifference in relation to the positive things of life.

So, Parkinsonism is not a 'side-effect' of neuroleptics, neither is it avoidable. Instead, Parkinsonism is the *core* therapeutic effect of neuroleptics: as reflected in the name, which refers to an agent which 'seizes' the nervous system and holds it constant (i.e. indifferent, blunted).[4] Demotivation should be regarded as inextricable from the neuroleptic form of tranquillization.[2] And the so-called 'negative symptoms' of schizophrenia are (in most instances) simply an inevitable consequence of neuroleptic treatment.[4]

By this account, the so-called 'atypical' neuroleptics (risperidone, olanzapine, quetiapine, etc.) are merely weaker Parkinsonism-inducing agents. The behaviour-controlling effect of 'atypicals' derives from inducing a somewhat milder form of Parkinsonism, combined with strong sedation.[11] However, clozapine is an exception, because clozapine is not a neuroleptic, does not induce Parkinsonism, and therefore (presumably) gets its behaviour-controlling therapeutic effect from sedation. The supposed benefit from clozapine of 'treating' the 'negative symptoms of schizophrenia' (such as de-motivation, lack of drive, asocial behaviour etc.) is therefore that—not being a neuroleptic—clozapine simply does not cause these negative symptoms.

What next?

Whatever the historical explanation for the wholesale misinterpretation of neuroleptic actions, recent high profile papers in the *New England Journal of Medicine*[12,13] and *JAMA*[14] have highlighted

serious problems with neuroleptics as a class (whether traditional or atypical), and the tide of opinion now seems to be turning against them.

In particular, the so-called 'atypical neuroleptics', which now take up 90% of the US market,[12] and are increasingly being prescribed to children,[6] seem to offer few advantages over the traditional agents[12] while being highly toxic and associated with significantly-increased mortality from metabolic and a variety of other causes.[13–16] These new data have added weight to the idea that usage of neuroleptics should now be severely restricted.[3,7,17]

Indeed, it looks as if after some 50 years widespread prescribing, there is going to be a massive re-evaluation and re-interpretation of these drugs, with a reversal of their evaluation as a great therapeutic breakthrough. It seems distinctly possible that for half a century, the creation of millions of asocial, neuroleptic-dependent but docile Parkinsonian patients has been misinterpreted as a 'cure' for schizophrenia. This wholesale re-interpretation represents an unprecedented disaster for the self-image and public reputation not just of psychiatry but of the whole medical profession.

Perhaps the main useful lesson from the emergence of the 'atypical' neuroleptics is that psychiatrists did not need to make all of their agitated and psychotic patients Parkinsonian in order to suppress their behaviour. 'Atypicals' are weakly neuroleptic but highly sedative. This implies that sedation is probably sufficient for behavioural control in most instances.[3,17] In the immediate term, it therefore seems plausible that already-existing, cheap, sedative drugs (such as benzodiazepines or antihistamines) offer realistic hope of being safer, equally effective and subjectively less-unpleasant substitutes for neuroleptics in many (if not all) patients.

I would argue that this should happen sooner rather than later. If we apply the test of choosing what treatment we would prefer for ourselves or our relatives with acute agitation or psychosis, knowing what we now know about neuroleptics, I think that many people (perhaps especially psychiatric professionals) would now wish to avoid neuroleptics except as a last resort. Few would be happy to wait a decade or so for the accumulations of a mass of randomized trial data (which may never emerge, since such trials would lack a commercial incentive) before making the choice of less dangerous and unpleasant drugs.[17]

But there is no hiding the fact that if neuroleptics were indeed to be replaced by sedatives, then this would seem like stepping-back half a century. It would entail an acknowledgement that psychiatry has been living in a chronic delusional state, and this may suggest that the same could apply to other branches of medicine. Since such a wholesale cognitive and organizational reappraisal is unlikely, perhaps the most realistic way that the desired change in practice will be accomplished is not by an explicit 'return' to old drugs but by the introduction of a novel (and patentable) class of sedatives which are marketed as having some kind of (more-or-less plausible) new therapeutic role.

Such a new class of tacit sedatives would enable the medical profession to continue its narrative of building-upon past progress, and retain its self-respect, albeit at the price of cognitive evasiveness. But, if such developments led to a major cut-back in neuroleptic prescriptions, then this deficiency of intellectual honesty would be a small price to pay.

Editor's note

For a counter-balancing view on the properties and use of neuroleptics, see the Commentary by Dr Daniels in this issue.[18]

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