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Building a House of Cards: The Dopamine Theory of Schizophrenia and Drug Action

By presenting a theory of schizophrenia suggesting that some or all of its symptoms are caused by a biochemical abnormality that antipsychotics happen to reverse, the dopamine hypothesis of schizophrenia is a key part of the story of how the group of drugs we are considering came to be understood as ‘miracle cures’—as drugs that target the basis of schizophrenia or psychosis. Although the inadequacy and inconsistency of the theory have been acknowledged ever since it was articulated, the dopamine hypothesis of schizophrenia has occupied research activity for decades and consumed vast amounts of funding. In fact, for many academics and practising clinicians, it has long moved beyond hypothesis into the realm of fact.

The original hypothesis proposed that schizophrenia is caused by over-activity of the brain chemical, dopamine. The theory has existed in many different versions, however, over the course of its life. Stephen Stahl, author of many best-selling textbooks on psychopharmacology, presents an elaborate version of the hypothesis in his 2008 book Antipsychotics and Mood Stabilisers. Backed up by numerous scientific-looking illustrations of brain circuits and neurons, he suggests that schizophrenia is caused by simultaneous over-activity of dopamine in one part of the brain, the limbic system, and under-activity in another, the cortex. Furthermore, he postulates that atypical antipsychotics simultaneously correct these opposing defects. No conflicting evidence is mentioned, and there is no acknowledgement of the implausibility of a situation involving opposing biochemical states co-existing in different, but inter-related, brain regions, or of the idea that one drug can simultaneously act in different ways in different areas (Stahl, 2008).

‘The history of schizophrenia research’, said pharmacologist Les Iverson in an interview with psychiatrist and academic David Healy,
‘is littered with the skeletons of chemical hypotheses’ (Iversen, 1998, p. 345). Before the dopamine hypothesis there was a thyroid hormone hypothesis of schizophrenia, a sex hormone hypothesis, the transmethylation and serotonin hypotheses, and many others. Since the 1990s glutamate has come into fashion, and interest in serotonin has been revived. The dopamine hypothesis seems to be the most persistent, however, but, in order to survive, it has had to absorb, transform or expel many awkward pieces of evidence. The popularity and longevity of the theory tells us something important about the vision psychiatry wishes to promote of itself and its treatments. The dopamine hypothesis of schizophrenia suggests, as many psychiatrists have wanted to believe for a long time, that psychiatric conditions are real diseases with tangible and specific biological origins, and that antipsychotic drugs constitute a genuine and innocuous medical treatment, which counteract the underlying defect in a highly targeted manner.

In fact, however, the dopamine theory was elaborated on the assumption that antipsychotic drugs act in a disease-specific way on the underlying pathology of schizophrenia or its symptoms. Because this view of antipsychotic action was already unquestioned, it was presumed that the origins of schizophrenia or psychosis could be deduced to be the opposite state from that produced by the drugs. So, according to a recent textbook of psychiatry, ‘the fact that every effective antipsychotic drug blocks dopamine D₂ receptors is powerful evidence of the importance of dopamine in the pathogenesis of schizophrenia’ (Wright et al., 2012, p. 272). Even in the early days of the dopamine hypothesis, few of its proponents seemed aware that they were making an assumption of this sort. The dopamine hypothesis of schizophrenia is a consequence of the fact that the disease-centred model had already eclipsed other ways of understanding drug action by the time the hypothesis was elaborated in the 1970s.

This chapter will demonstrate that decades of research have failed to provide evidence that the symptoms of either schizophrenia or psychosis result from an underlying abnormality of dopamine activity. What research has clearly demonstrated, in contrast, is that antipsychotic drugs disturb dopamine function to a greater or lesser extent, and that their action on the dopamine system is responsible for many of the characteristic neurological disturbances they produce. The dopamine theory of schizophrenia has, however, helped to ensure that such effects are decisively relegated to the place of second fiddle behind the drugs’ proposed ability to rectify the underlying disease. In this way, the dopamine hypothesis provided an important bulwark against the