Schizophrenia, Antipsychotic Medication and Mortality

Written by Professor Brendan Kelly, Professor of Psychiatry, Trinity College Dublin

I am not a regular reader of *Elle* magazine. In fact, I don't think I ever bought a copy until, some years ago, I came across an extraordinary essay about the side-effects of antipsychotic medication, published in *Elle* in 2011.[1] Written by Lauren Slater, the article is titled 'Killing my body to save my mind'. In the piece, Slater describes her treatment for depression with psychotic features. More precisely, Slater explores the effects of the antipsychotic medication olanzapine in some detail. Her essay is well worth a read. I routinely recommend it to medical students and post-graduate trainees in psychiatry.

Slater's view is balanced, insightful, and – best of all - informed by personal experience. Suffering with severe psychotic depression, Slater writes that the therapeutic effect of olanzapine was rapid and undeniable. Adding olanzapine to her prescription lifted her symptoms within days. Slater is unequivocal and emphatic: olanzapine saved her life.

But Slater is also unequivocal about something else: olanzapine led to weight gain. This is very problematic for many people, not just Slater. This kind of adverse effect is not only distressing in itself, but also carries risks to physical health, as Slater points out. I see this in my clinical practice all the time: people gain weight on certain medications and often struggle to lose it. Paying attention to diet and exercise helps to manage this problem, but does not always solve it fully. As many people know from their own lives, it can be difficult to shift unwanted weight.

So, what to do? Slater is clear about the risk-benefit balance in her case: despite the side effects of olanzapine, she remains tremendously grateful to be free of her symptoms of psychotic depression. She takes the olanzapine.

But this is a trade-off that many people face and I have often wondered if the adverse effects of some of these medications outweigh the benefits, especially in schizophrenia. We know that antipsychotic medication is effective in alleviating symptoms of schizophrenia, reducing relapse rates, and therefore increasing quality of life.[2] But what about *quantity* of life? To put it bluntly: if some antipsychotic medications lead to increased

weight, heightened risk of diabetes and high cholesterol, do they also increase the risk of heart disease or early death? If there is such an effect, might it out-weigh the antipsychotic benefits of these medications?

This is a hugely important question. The clear benefits of antipsychotics are not to be forgone lightly. As a result, there has been a great deal of research on this issue in the context of schizophrenia, the condition for which antipsychotics are most commonly prescribed. Is there net benefit or net harm from these medications?

In 2013, Casey Crump and colleagues published a paper in the *American Journal of Psychiatry* detailing the experiences of over six million Swedish adults, including 8,277 with schizophrenia, over the course of seven years.[3] They looked at risk of death during this period in these two groups: those with schizophrenia and those without. These researchers found that, on average, men with schizophrenia die 15 years earlier, and women 12 years earlier, than the rest of the population. This is not explained by unnatural deaths: the leading causes of death are heart disease and cancer. At first glance, this appears to confirm our worst fears: might antipsychotic medication contribute to this increased risk of dying from heart disease among people with schizophrenia?

Crump and colleagues, however, note something very interesting in their data: in this population, *lack* of antipsychotic treatment is associated with increased mortality. In other words, *not* being on an antipsychotic medication is linked with elevated risk of dying over the seven-year period studied. This is, perhaps, the opposite of what we might have expected, given the side effects of certain antipsychotics. It appears that antipsychotic medications are associated with reduced rather than increased risk of death over seven years. Is this true? If so, it is a strong endorsement of the broader benefits of antipsychotic treatment.

In 2020, a much larger study from Finland provided further clarity - and good news – on this issue.[4] Researchers in Finland followed up some 62,250 patients with schizophrenia for a median of 14 years to study illness and risk of death in relation to antipsychotic treatment. Critically, their analysis takes account of other variables that might impact on mortality (e.g. age, gender, other illnesses, different medications, etc.). The results are dramatic, and strongly support the findings of Crump and colleagues. Patients who are on antipsychotic medication have half the risk of dying over the next 14 years compared to those who do not receive antipsychotics. This includes significantly lower risks of death from heart disease as well as suicide. These benefits are especially pronounced with clozapine, the antipsychotic medication used for treatment-resistant schizophrenia.

This is very compelling evidence in favour of antipsychotic medication. To put these findings another way, the cumulative death rates in the Finnish study were 46 per cent for people with schizophrenia who were not on antipsychotics, 26 per cent for those on any antipsychotic, and 16 per cent for those on clozapine. These are enormous differences. As the study authors conclude, the findings suggest that, far from increasing risk of death, long-term antipsychotic use is associated with substantially *decreased* mortality in schizophrenia, especially among patients treated with clozapine.

To summarise: antipsychotic medication reduces symptoms of schizophrenia and, despite its side effects, is associated with *decreased* risks of premature death from physical illness (such as heart disease) and suicide. This is not to say that everyone responds equally well to antipsychotic medication: certain medications help some people more than others. Side effects also differ between medications and between people, as do individual judgements about the balance of benefits and risks. Reaching informed agreement on these issues requires both good research information and strong therapeutic relationships between patients and health professionals. Moreover, people change over time, and so do their mental health needs. Again, dialogue is vital if we are to use therapeutic tools such as medication to their best advantage.

There are also other therapeutic tools, in addition to medication, that we can use when indicated. Psychological and social care are essential elements of treatment in schizophrenia, as they are in most mental illnesses. We neglect these to our detriment.

In the first instance, psycho-education for patient and family helps to develop understandings of the illness and its treatment, and enhances the therapeutic alliance between patient, family and health-care providers. Other psychological approaches of proven benefit for certain people include cognitive-behaviour therapy (CBT), family interventions, art therapy (especially for negative symptoms), self-help groups and peer-support. These treatments and resources are not always available in all areas, but they can make substantial contributions to care when they can be sourced.

There is particular interest in CBT for certain people with schizophrenia, focusing on helping them deal with persistent delusions and hallucinations; establishing links between thoughts, feelings, actions, symptoms and functioning; and re-evaluating other people's perceptions, beliefs or reasoning as they relate to target symptoms. CBT can involve monitoring one's own thoughts, feelings or behaviours with respect to symptoms; promoting alternative coping strategies; diminishing distress, and improving functioning. Used well, CBT can be very effective.

Social interventions are also important in schizophrenia. The precise steps to be taken depend on individual circumstances. Interventions can include assessment of social and occupational needs, provision of information and training, and advice on financial and practical matters relating to housing, occupation and social function. Many people with schizophrenia experience particular difficulty obtaining and sustaining accommodation. It is important to ensure that housing is appropriate to the needs of the person and that there are no preventable psycho-social stressors likely to hinder treatment or hamper recovery.

Occupational therapy can play a vital role for many people with schizophrenia, especially those with recurring episodes of psychosis. Education, training and employment all support recovery from episodes of illness and long-term maintenance of good mental health. Day hospitals and day centres provide a useful focus for many, as well as opportunity for detailed clinical assessment and liaison with family and carers. Social work supports all of these interventions, as well as identifying and helping resolve family and carer stress, which can be a significant problem in schizophrenia.

Brendan Kelly is Professor of Psychiatry at Trinity College Dublin and author of "In Search of Madness: A Psychiatrist's Travels Through the History of Mental Illness" (Gill Books, 2022).

References

1. Slater L. Killing my body to save my mind. Elle, 15 August 2011. https://www.elle.com/beauty/health-fitness/advice/a11743/gaining-weight-to-cure-depression/ (Accessed 7 March 2022).
2. Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. British Journal of Psychiatry 2012; 200: 97-106. https://doi.org/10.1192/bjp.bp.111.096594
3. Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. American Journal of Psychiatry 2013; 170: 324-33. https://doi.org/10.1176/appi.ajp.2012.12050599
4. Taipale H, Tanskanen A, Mehtälä J, Vattulainen P, Correll CU, Tiihonen J. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). World Psychiatry 2020; 19: 61-8. https://doi.org/10.1002/wps.20699