COMMENTARY

DATA DON'T SPEAK FOR THEMSELVES. ALTERNATIVE EXPLANATIONS FOR LONG-TERM USE OF PSYCHIATRIC DRUGS

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The data reported by Gøtzsche in this issue of *Clinical Neuropsychiatry* show that the percentage of Danish users who redeemed a prescription for the same or a similar drug in each of the ten years between 2007 and 2017 was 18% for benzodiazepines, 29% for stimulants, and 40% for lithium. In a previous paper (Gøtzsche, 2020), Gøtzsche had reported similar data for antipsychotics and antidepressants (35% and 33%, respectively). Gøtzsche concludes that: "*No matter which psychiatric drug people take or what their problem is, roughly one-third of the patients will still be in treatment with the same drug or a similar one ten years later.*" Considering the size of the database and the duration of the follow-up, these findings are much relevant and require an explanation. The explanation given by Gøtzsche is categorical and based on the sinister combination of business and malpractice: "*Psychiatric drug usage is mainly driven by commercial pressures*", "*systematic deception is an important reason why drug usage continues for many years*", *"[patients] are not told that what they perceive as a drug effect is likely to be the spontaneous improvement that would have occurred in any case*."

In this commentary, I will argue that Gøtzsche fails to consider alternative explanations that are based on clinical reflections focusing on approved indications for psychiatric drugs, their use in the "real world", and the validity of psychiatric diagnoses.

Alternative explanations for long-term use of lithium and stimulants are straightforward. Lithium is a mood stabilizer that is used mainly for the management of bipolar disorder. International guidelines recommend long-term lithium therapy not only to treat acute mania and bipolar depression but also to prevent recurrence and reduce the risk of suicide (Mahli et al., 2017). Long-term (but not short-term) lithium therapy is associated with decreased risk of suicide whereas lithium discontinuation is associated with an increased suicide risk (Del Matto et al., 2020). Based on these data, it is understandable why clinicians prescribe long-term lithium therapy. The hypothesis that commercial pressures influence their decision to prescribe lithium is unlikely if one looks at the pharmaceutical industry's massive promotion of alternative and more lucrative mood stabilizers (Licht, 2012). Psychostimulants (N06BA, centrally acting sympathomimetics) are used to treat attention deficit hyperactivity disorder (ADHD) and narcolepsy. In most cases, these conditions are chronic and, when drug treatment is prescribed, patients need to take medications for long time. In conclusion, assuming that prescribers followed the approved indications for lithium and stimulants, the percentages reported by Gøtzsche are not surprising. If anything, it would be interesting to know why the majority of patients stopped treatment (full recovery? low adherence? side effects? switch to other drugs?).

Explanations for long-term use of benzodiazepines, antipsychotics, and antidepressants are more complex and highlight the theoretical and clinical weakness of contemporary psychiatry. Unlike lithium and stimulants which have specific indications, benzodiazepines, antipsychotics, and antidepressants are prescribed in patients with a variety of psychiatric disorders. For example, SSRIs (selective serotonin reuptake inhibitors) are included in the class of antidepressants but they are widely prescribed for anxiety disorders, obsessive-compulsive disorder, bulimia nervosa, and trauma and stressor-related disorders. SGAs (second generation antipsychotics) are increasingly used as mood stabilizers in bipolar disorder and to treat behavioral disturbances associated with cognitive decline. Benzodiazepines are frequently associated with other psychiatric drugs to treat patients with different diagnoses and anxiety, which is a ubiquitous symptom in psychiatric disorders. This means that population-based data describing the use of psychiatric drugs (such as those reported by Gøtzsche for benzodiazepines, antipsychotics, and

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antidepressants) are not useful to infer the diagnostic status of people taking them. Without knowing the diagnosis and the nuances of the clinical picture (see below), it is problematic to judge the appropriateness of long-term therapy.

A related problem is the poor validity of psychiatric diagnoses which reflect syndromes, not diseases. Gøtzsche seems to ignore this crucial point when he states "*the main indication for antipsychotics is schizophrenia, which has traditionally been perceived as a chronic condition, whereas the main indication for antidepressants is depression, which has been perceived as episodic.*" The diagnostic labels of "schizophrenia" and "depression" are likely to include a variety of different disorders with different etiology, pathogenesis, natural course, prognosis, and response to treatment. To say that schizophrenia is chronic and depression is episodic is an oversimplification that have three negative implications: (1) it disregards the complexity of individual cases; (2) it reifies the status of schizophrenia and depression as disease entities; and (3) it could strengthen the wrong belief that categorical diagnoses (DSM or ICD-like) are a scientifically sound basis to choose the type and duration of drug therapy.

Another possible explanation for long-term therapies is the limited efficacy of psychiatric drugs. If we had drugs that would cause a rapid and full recovery as it is the case in other fields of medicine (e.g. infectious diseases), long-term therapies would be pointless. Yet, if the patient continues to present symptoms in spite of ongoing treatment, the clinician is forced to try alternative treatments, often choosing drugs from the same pharmacological class. This happens often with antidepressants, as shown, for example, by a critical analysis of the findings of the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study (Pigott et al., 2010). Partial response, high frequency of relapse, and persistence of residual symptoms are common in depressive syndromes, which can explain repeated and long-term prescription of antidepressant drugs. Gøtzsche argues that "*systematic deception is an important reason why drug usage continues for many years*". My view instead is that clinicians pay the price of treating heterogeneous syndromes with one-fits-all drugs. As clearly stated by Gordon Parker: "*if the sample studied is weighted to those with a biological melancholic depression, then superiority of an antidepressant drug to placebo might be expected. If the sample principally comprises those with personality styles that cause them to see themselves, the world and their future negatively, the superiority of cognitive-behavioural therapy might be anticipated, and an antidepressant might be quantified as ineffective. If the sample largely includes those with stress-induced 'reactive depressive' disorders, then empathic counselling plus strategies that neutralise or minimise the stressor and/or assist the individual to come to terms with it are appropriate, and an antidepressant might be of questionable benefit. Yet major depression welcomes all these subtypes to its family*." (Parker, 2018, p. 455).

Gøtzsche should be commended for collecting and publishing large-scale data that unveil an important aspect of drug use in psychiatry. Yet, his one-sided interpretation of the data risks to weaken the credibility of the growing campaign against the undue influence of pharmaceutical industry over medicine and psychiatry (Badcott, 2013).

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