DSM and ICD operational criteria. According to the DSM-5, the core features of depression are depressed mood and anhedonia. ICD-10 adds a third core item, "decreased energy or increased fatigue". These core features have been identified clinically to be central to depression and are included in the six-item version of the Hamilton Depression Rating Scale, along with guilt feelings, psychic anxiety and psychomotor retardation[7]. This scale is clinically and psychometrically valid, but does not characterize phenomenologically the three core features. These features may also identify three subtypes of depression, marked predominantly by depressed mood, anhedonia or decreased energy/increased fatigue, respectively.

However, such potential subtypes of depression have been studied rarely, partly due to the fact that the core items of depression have not been clearly operationalized. The ICD-10 Diagnostic Criteria for Research state that depressed mood should be "to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances (non-reactivity), and sustained for at least 2 weeks". This wording is partly replicated in the ICD-10 itself: "The lowered mood varies little from day to day, and is often unresponsive to circumstances, yet may show a characteristic diurnal variation". The DSM-5 requires depressed mood to be present "most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others". Anhedonia has also been seldom studied, partly due to its inconsistent conceptualization in depression[8]. Aspects of anhedonia (e.g., low interest-activity), have been found to predict poor antidepressant outcome and prolonged time to remission[8]. Analogously, although psychomotor disturbances may have prognostic implications, explicit definitions of psychomotor phenomena remain elusive[9].

We are currently developing and testing the applicability of a new diagnostic assessment of depression, which focuses on the phenomenology of the core features of the syndrome according to ICD-10 and DSM-5 (depressed mood, anhedonia, and decreased energy), the CORE Interview. We propose that an increased emphasis on the phenomenology of the core items will improve the validity of the diagnosis of depression and help to identify clinically meaningful subtypes. A more specific diagnosis can help clinicians identify the patients who are more likely to benefit from certain types of antidepressant treatment and improve the search for genes and biomarkers for mood disorders.

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DOI:10.1002/wps.20461

Who are excellent lithium responders and why do they matter?

After more than six decades of use in modern psychiatry, lithium remains one of the first-line treatments for prevention of manic and depressive recurrences of bipolar disorder. A number of longitudinal observations report remarkably similar response rates of about 30%, although this estimate is probably influenced by non-compliance in some patients[1]. Some of those people who stabilize on lithium particularly well have been called excellent, full or complete responders[2]. These patients not only cease experiencing further mood episodes, but also return to their pre-illness level of functioning.

This raises a question as to where these patients fit in the current diagnostic classification. Robins and Guze proposed five criteria to delineate a diagnostically valid disorder in psychiatry, including clinical description, laboratory studies (biological markers), delimitation from other disorders, stability of diagnosis at follow-up, and family studies (familial nature of the condition)[3]. Lithium responders have distinct clinical features that largely fit these criteria and thus might constitute a distinct diagnostic category[4].

Their treatment response is stable in the long term[5], they present with a typical recurrent episodic illness and relatively fewer comorbidities[6], and their affected relatives often respond to lithium as well[7]. The episodic pattern of the clinical course, which is among the strongest correlates of lithium response, is also familial[8]. There are also accumulating data on biological markers specific to these patients and differentiating them from lithium non-responders, including most recently data from studies of neurons derived from induced pluripotent stem cells[9]. Hence, compared to other psychiatric conditions, lithium responsive bipolar disorder appears to be a narrower, more homogeneous and highly heritable phenotype. Distinguishing this phenotype from the rest of mood disorders has both clinical and heuristic value.

Clinically, many lithium responders do not stabilize on other treatments; when they are unable to stay on lithium, for instance because of poor tolerability, finding an effective replacement often becomes difficult[10]. The search for clinical predictors of lithium response is still going on, but several factors are emerging repeatedly out of different studies. The key features are the episodic recurrent clinical course and the family history of bipolar disorder, especially lithium responsive bipolar disorder[7]. However, more accurate clinical and biological predictors of lith-

ium response still need to be introduced into clinical practice; as more options for long-term treatment of bipolar disorder are available, it is crucial to help clinicians select the right treatment for individual patients.

At the same time, there are many open questions that deserve further study. Among them are uncertainties about the time to response. Clinically some people improve after few days, while others need several months to stabilize. This has led some to suggest that the morbidity in the first year of treatment may not be completely predictive of long-term outcome. Robust predictors of excellent response will help deciding in specific cases for how long a lithium trial needs to extend.

Recognition of lithium responders as a specific form of bipolar disorder has also implications for planning of clinical services. For instance, clinical programs that provide primarily one-time consultations or only short-term follow-up are at a higher risk of missing these patients. Additionally, the tendency to use unnecessary drug combinations can be damaging, obscure the clinical presentation and lead to treatment refractoriness. As a result, a number of potential responders may receive suboptimal treatment, paradoxically sometimes even in specialty programs.

From the research point of view, it is valuable to study a medication that works fully in a proportion of patients rather than drugs that are partially effective in almost everybody. The specificity and the quality of the response suggest that the pharmacodynamic effects of lithium may provide important clues about the neurobiology of bipolar disorder. However, it is not easy to determine which of the multitude of lithium's actions is responsible for its episode preventing effect. A number of mechanisms have been postulated, from changes in electrolyte balance, membrane transport, interaction with various elements of second messenger system, calcium signaling, to chronobiological changes and neuroprotective effects[4].

Clinical research findings in lithium responders also challenge certain concepts of bipolar disorder. For instance, contrary to the now popular staging model, the excellent response in this group does not seem to diminish with treatment delay or with the duration of the illness[5]. The narrow phenotypic spectrum in these patients (and their families) is at odds with the notion of the common comorbidity of bipolar disorder with many other psychiatric disorders and their shared genetic underpinnings.

At the same time, the higher genetic risk and familial nature of the treatment response make this group a promising target for molecular genetic investigations. These started with linkage analyses and association studies of candidate genes; then the field turned towards genome-wide association analyses. Once replicated, genome-wide analyses may provide clinically applicable tools such as polygenic risk scores to guide selection of long-term treatment.

Most recently, several studies confirmed the specificity of lithium response in a novel cellular model of bipolar disorder. Neurons derived from induced pluripotent stem cells of people with bipolar disorder were hyperexcitable in comparison with neurons from healthy controls. This hyperexcitability could be attenuated by *in vitro* lithium treatment, but only in cells from people who responded to lithium clinically, not in cells from non-responders[9].

Over the last 20 years, lithium has become a less commonly used option in the long-term treatment of bipolar disorder. Many physicians now consider it a difficult medication to use. Yet, the excellent responders are a reminder that there is a group of patients for whom lithium is not only the best, but perhaps the only treatment option. For this reason alone, they deserve our clinical and research attention.

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DOI:10.1002/wps.20462