

DSM-5's Impact on Psychiatric Clinical Trials: Challenges and Opportunities

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is considered to be the standard for diagnostic criteria of psychiatric disorders, and the DSM-IV-Text Revision (TR) is extensively used by a broad range of international healthcare professionals in a wide variety of clinical and research settings. The DSM is also extensively utilised in a variety of psychiatric clinical trials, and is relied upon heavily by regulatory agencies for labelling purposes. In recent years, the DSM-5 Task Force and Work Group members have been labouring to revise DSM-IV-TR criteria to reflect recent advances in the science and conceptualisation of mental disorders. This brief review will summarise some of the more salient proposed criteria revisions, their implications for psychiatric trials, and resultant opportunities for psychiatric drug developers.

Although it is impossible to predict the exact criteria that will be part of the final DSM-5, it is important for psychiatry drug developers to closely monitor the progress of DSM-5, and to make adjustments that incorporate applicable revisions in their development programmes. There is some urgency to this task, as Phase 1 field trials are currently underway and members of the DSM-5 Task Force and Work Group have already disseminated initial text revisions of the DSM-5 for public review. In the spring of 2011, revisions to these proposed criteria (based on results from the first phase of field trials) will be tested again in a second phase of field trials, culminating in the publication of DSM-5 at APA's 2013 Annual Meeting in San Francisco¹. Given the length of psychiatric drug development programmes, the implementation of DSM-5 will undoubtedly have near-term ramifications in terms of trial conduct (from diagnostic schemas to endpoints and scales), regulatory appraisal, and even the potential marketing of pharmaceutical products to physicians and patients.

DSM-5 draft criteria revisions have already been suggested for numerous drug treatment indications, including substance-related disorders, schizophrenia and other psychotic disorders, mood and anxiety disorders, eating and sleep disorders, and delirium, dementia, amnesia, and other cognitive disorders. Some of these changes will involve patients currently diagnosed with one disorder being classified elsewhere, while other changes may serve to provide only clarification. For example, in the revised criteria for schizophrenia, the former DSM-IV-TR subtypes of disorganised, paranoid, undifferentiated, and residual schizophrenia (which have been used extensively in both acute and chronic schizophrenia trials for inclusion purposes) may be abandoned in favour of various symptoms or "dimensions", such as hallucinations, delusions, disorganisation, restricted emotional expression, avolition, impaired cognition, depression, and mania.

Although there may be some difficulties in making comparisons to traditional DSM-IV-TR criteria, the use of "dimensions"

may actually increase the validity of certain diagnostic criteria and provide a more multidimensional and holistic assessment of a patient's condition, including disease severity, functional level, and quality of life. Adding dimensions to diagnostic criteria will also necessitate the design and validation of novel and more complex outcome measures and improved patient-reported outcomes. This feature of DSM-5 should also result in better concordance between DSM and ICD, with improvement in comparability of data obtained from clinical trials in different regions of the world.

As another example, the concept of "catatonia" is likely to be removed from the new schizophrenia criteria, and may become a diagnostic class within psychosis, or a specifier to psychosis or mood disorders. Therefore, some schizophrenics will be reclassified. Reclassifying catatonia outside schizophrenia could potentially open the way for novel drugs, as the optimal treatment for catatonia is likely to differ from the standard treatment for schizophrenia. For example, dopamine D2 blockade (the current standard drug therapy for schizophrenia) may be contraindicated in a new drug treatment claim for catatonia.

The DSM-5 work group is considering adding a novel criteria related to "Psychosis Risk Syndrome", which is characterised by a progressive and distressing (but attenuated) form of delusions, hallucinations, and disorganised speech, despite intact reality testing. The concept of a risk syndrome that precedes the full-blown disorder has been well accepted in other disciplines, and in some CNS disorders such as Alzheimer's disease. Although controversial (primarily due to stigmatisation and the possibility of false positive diagnosis), if validated this syndrome may advance trials in high-risk individuals and form the basis for a new drug treatment claim. Recent studies of long-chain fatty acids have supported the value of treating at-risk patients by reducing progression to psychotic disorders in young people with sub-threshold psychotic states².

The DSM-5 may also include a new diagnostic criterion for "Mixed Anxiety Depression", in which the patient has three or four of the symptoms of major depression (which must include depressed mood and/or anhedonia) accompanied by anxious distress (which must include two or more of the following symptoms: irrational worry, preoccupation with unpleasant worries, trouble relaxing, motor tension, and fear that something awful may happen). These symptoms must have lasted at least two weeks with no other DSM diagnosis of anxiety or depression present, and both must occur at the same time. There is some obvious face validity to this construct, which benefits from wide acceptance by practicing clinicians and depression researchers, who have long noted anxiety as a predictor of poor response to antidepressants³ and future suicide behaviour⁴. Obviously, there is a need for effective treatments for comorbid anxiety in both unipolar and bipolar depression, and many depression clinical trials have already begun permitting subjects with comorbid anxiety diagnosis/symptoms



into treatment trials, and vice versa. This novel categorisation may promote drug discovery, as well as a re-examination of existing drug candidates such as prazocin, modanfinil and n-acetyl-cysteine, which have all shown some utility in alleviating mixed anxiety and depression symptoms.

A last example of the many proposed revisions to DSM includes the recommendation that the category “Delirium, Dementia, Amnesic and other Cognitive Disorders” be divided into three broader syndromes: “Delirium”, “Major Neurocognitive Disorders”, and “Minor Neurocognitive Disorders”, with no mention of Dementia. In order to meet diagnostic criteria for major neurocognitive disorder, objective assessments must show clear deficits in the relevant cognitive domain (typically > 2.0 standard deviations below the mean of an appropriate reference population), while minor cognitive disorders would be characterised by mild deficits during these assessments (typically 1 to 2.0 standard deviations below the mean of an appropriate reference population). This would require the validation of novel neuropsychological tests (and accompanying independent functional impairment measures) with acceptable sensitivity and reliability, as well as standardised statistical methodologies for choosing relevant cognitive domains. This new classification could sanction the long sought-after indication of “Mild Cognitive Impairment”, and expand the development of various nootropics designed to enhance cognition across an assortment of minor cognitive disorders that could be targets for new drug treatment claims.

As a final point, it should be noted that there has been a long evolution of labelling for psychiatric drugs that has been implicitly tied to ever-changing diagnostic classification systems, and international regulatory agencies will undoubtedly need to consider future arguments of new drug treatment claims and outcome measures based on DSM-5. However, this evolution is guided not only by changes in diagnostic classification, but also by relevance to public health, the practice of

psychiatry, and clinical meaningfulness to the patients⁵.

References:

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