# Developing Classification in Psychiatry – Implications of 50 Years of Progress in Psychopharmacological Therapeutics

*a report by*
**Graham Mellsop** *and* **Selim El-Badri**

*Professor, Waikato Clinical School, University of Auckland, and Community Psychiatrist, Waikato District Health Board*

DOI:10.17925/ENR.2006.00.01.83

Forty years ago, after a spate of pharmacological discoveries, diagnostic confidence was rising in psychiatry. Textbooks of the time indicated that the work of Pinel, Kraepelin and Bleuler had laid the foundation for imminent and encouraging progress in clarifying the connections between aetiology (or at least pathogenesis), classificatory (diagnostic) labels and largely pharmacologically based therapeutic choices.[1] This could be seen within the framework of 'natural' and 'categorical' classifications as clarified by Pichot.[2] He considered that, in science, the 'natural' classifications were those that allow the maximum number of predictions.

With the criteria set out by Robins and Guze,[3] psychiatry felt confident of validating its diagnostic groupings and refining the relationship between, for example, schizophrenia and neuroleptics; depression and antidepressants; bipolar disorders and lithium; anxiety and anxiolytics; and anorexia nervosa and family therapy, i.e. diagnoses predicting treatment. The missing links in the understanding of both classifications and therapies were expected to be filled in with all of the promising developing research, particularly with better clinical, cohort and other longitudinal studies, neurobiological developments and psychopharmacological fine-tuning.

## Antipsychotics and the Treatment of Psychiatric Disorders

The introduction of chlorpromazine in the 1950s and the subsequent development of other related phenothiazines, now referred to as conventional antipsychotics, provided a resurgence of interest in the pathogenesis and treatment of psychiatric disorders, particularly schizophrenia. Knowledge of the actions of such agents has significantly stimulated research in biological psychiatry aimed at defining patho-physiological abnormalities. The discovery of dopaminergic receptor-blocking capabilities of conventional antipsychotic drugs led to the dopamine hypothesis of schizophrenia.[4] Conventional anti-psychotics were found to be effective in controlling psychotic symptoms, such as hallucinations, delusions and agitation, and in reducing both morbidity and mortality. However, they have significant side effects, such as extrapyramidal symptoms. Atypical antipsychotics were introduced in the last two decades and have led to dramatic shifts in the treatment of major mental illness. They offer physicians the ability to treat patients with schizophrenia and bipolar/mania with less of the adverse effects of the conventional antipsychotics. This is because they have affinity for the serotonergic neurotransmitter system in addition to their effects on the dopamine D2 receptor. This affinity may explain their clinical profile of lower extrapyramidal symptoms and improvement in cognition.[5] On account of this, adherence to treatment is enhanced. Atypical antipsychotics – clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole – are being prescribed for schizophrenia, bipolar disorder and related psychoses at ever-increasing rates because of their beneficial side effect profiles and, in the case of clozapine, superior efficacy in treatment-resistant disorder. Several new formulations of atypical neuroleptics have become available, including liquid, orally disintegrating tablets and rapid-acting and long-acting intramuscular preparations.

Graham Mellsop is a Professor at the Waikato Clinical School of the University of Auckland. He has held professorial positions with the Universities of Otago, Queensland and Melbourne. Professor Mellsop is on the board of the World Psychiatric Association and is involved in working parties considering aspects of the next version of the International Classification of Diseases (ICD). His published research areas include epidemiology, psychopharmacology, medical education, classification in psychiatry and aspects of mental health service delivery.

Selim El-Badri is a Community Psychiatrist at the Waikato District Health Board. Prior to going to New Zealand in 1998, he worked in England and Ireland as, for example, Clinical Research Associate. Dr El-Badri's clinical work is focused on general adult psychiatry and the treatment of people with mental illness in a multidisciplinary and community-orientated setting. His research areas include neurobiological changes in bipolar mood disorder, in-patient aggressive behaviour, the use of seclusion and the experience of stigma among patients with mental illness.

1. *Mayer-Gross W, Slater E, Roth M,* Clinical Psychiatry*, Baillière, Tindall and Cassell, London (1960).*
2. *Pichot P, "Nosological Developments in European Psychiatry and Psychopharmacology",* Pharmacopsychiatry *(1986);19: pp. 23–25.*
3. *Robins E, Guze S B, "Establishment of Diagnostic Validity in Psychiatric Illness: Its Application to Schizophrenia",* Am J Psychiatry *(1970);126: pp. 983–986.*
4. *Kahn R S, Davis K L, "New Developments in Dopamine and Schizophrenia", in: Bloom F E, Kupfer D J (eds.)* Psychopharmacology: The Fourth Generation of Progress*, Raven Press, New York (1995); pp. 119–204.*
5. *Stahl S M,* Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*, 2nd edition, Cambridge University Press, Cambridge (2000); pp. 414–425.*

However, in the last ten years, the links between diagnoses and pharmacology have become less clear, and the earlier optimism would appear to have been a little premature.

## Polypharmacy

Partly empirically and partly driven by the recognition that schizophrenia may be associated with abnormalities of multiple neurotransmitter systems – including dopamine, serotonin, gamma-aminobutyric acid and glutamate – polypharmacy has gained respectability.[6] Practice guidelines promote a multimodal treatment approach incorporating the biopsychosocial model.[7] Therefore, in addition to psychosocial interventions, the ideal treatment for schizophrenia may not be a single pharmacological agent, but several agents that match the different expressions of the illness. Furthermore, depression is also a common and important feature of schizophrenia and may be related to a variety of factors,[8] so it is not surprising that the International Classification of Diseases (ICD)-10 recognises post-schizophrenic depression as a distinct subtype of schizophrenia.[9]

Similarly, over the past few decades, the psychopharmacology of depression has evolved rapidly. First-generation antidepressant medications – tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)-enhanced serotonergic or noradrenergic mechanisms or both.[10] However, TCAs were associated with adverse effects related to their antihistaminic, anticholinergic and anti-alpha1-adrenergic effects. The second generation of antidepressants have been designed to target or interact with specific single receptors or with more than one receptor site without interacting with histaminic and cholinergic or adrenergic receptors. They are less likely to cause side effects, such as dry mouth, hypotension and sedation.[10] Paralleling this has been the classificatory ability to take account of wider contextual issues that affect clinical decision-making.

Treatment guidelines for schizophrenia now include the use of neuroleptics, antidepressants, benzodiazepines, mood stabilisers, family education, psychotherapy, cognitive behavioural therapy (CBT) and electroconvulsive treatment (ECT).[7] The treatment guidelines for depression include almost all the same categories (antidepressants, neuroleptics, CBT, ECT, mood stabilisers, family work and psycho education).[11,12] Many of the same therapeutic approaches also appear in guidelines for the various anxiety spectrum disorders, for example, in obsessive-compulsive disorders.[13] In other words, the simple relationships that had been expected, arising from developments of aetiological or pathogenetic-based classifications and 'magic

*The dissonance between diagnosis and prescription has gradually become more obvious. The question is how the recognition of this dissonance can be used to further improve clinical practice.*


6. *Owen F, Simpson M D C, "The Neurochemistry of Schizophrenia", in: Hisrch S R, Weinberger D R (eds),* Schizophrenia, *Blackwell Science, Oxford (1995); pp. 358–378.*
7. *National Collaborating Centre for Mental Health,* Schizophrenia: Full National Clinical Guideline on Core Interventions in Primary and Secondary Care, *Gaskell, the British Psychological Society, London (2003).*
8. *Furtado V A, Srihari V, "Atypical Antipsychotics for People with Both Schizophrenia and Depression" (protocol),* Cochrane Database Syst Rev *(2005);3: CD005377.*
9. *World Health Organization,* The ICD10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines *(1992).*
10. *Feighner J P, "Mechanism of Action of Antidepressant Medication",* J Clin Psychiatry *(1999);60(suppl 4): pp. 4–11.*
11. *National Collaborating Centre for Mental Health,* Depression: Full National Clinical Guideline on the Management of Depression in Primary and Secondary Care, *Gaskell, the British Psychological Society, London (2004).*
12. *Frangou S, "Advancing the Pharmacological Treatment of Bipolar Depression",* Adv Psychiatr Treat *(2005);11: pp. 28–37.*
13. *Goodman W K, "Pharmacotherapy of OCD", In: Stein D J, Hollander E (ed),* Textbook of Anxiety Disorders, *American Psychiatric Publishing, Washington DC (2002).*

bullets', had failed because of the multifactorial nature of complex mental processes. There was not a one-to-one illness-treatment relationship. Multiple other consumer and contextual characteristics influence the clinical management plans and treatment choices.[14,15]

## Improving Classification

Optimism and pessimism are both consequences of the above, optimism because of the constant increase in therapeutic possibilities and pessimism because the therapeutic 'magic bullets' have not appeared. If there is an increasing divergence between the psychiatric disorder labels (classification) and the pharmaceutical prescriptions to be applied, that must raise some questions about the validity of the standard classificatory systems, such as the International Classification of Diseases, Tenth Revision (ICD-10) and at least axis one of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV).[9] The dissonance between diagnosis and prescription has gradually become more obvious. The question is how the recognition of this dissonance can be used to further improve clinical practice. It may well be that the aims, structure or function of the classificatory schemata should be overhauled.

It has been acknowledged that the use of strict categorical criteria to formulate a 'global diagnostic construct' will ultimately exclude patients who do not meet such criteria and, hence, the need to broaden the diagnostic process so that the symptom profile includes dimensions involving, for example, motor, cognition and emotional performance that can be observed not only in depression, but in a number of neuropsychiatric disorders.[15–17] Therefore, a change of emphasis in terms of treatment modalities is also required to match different expressions of these disorders and other aspects of functionality. Most importantly, there is a need to focus on both symptoms suppression and measures aimed at enhancing global functioning.[14–17]

Work that has aimed to use patient characteristics to predict cost of care (so-called casemix classifications) has also revealed a surprisingly small contribution of the diagnostic label to the physician's cost-incurring management decisions.[18–20] This provides a further hint that if the classificatory systems are expected to be useful, there is significant room for improvement.

Studies to clarify cost-predicting patient characteristics and care-seeking characteristics have found a number of variables to be relevant, for example:

- a patient's age;
- legal status;
- ethnicity;
- level of disability; and
- standardised assessment, with a broad range of clinical variables.[18–22]

Clinical practice guidelines issued by professional bodies in a number of countries also refer to many characteristics of the patient, or of the episode of care, that influence pharmaceutical prescribing, for example:

- a patient's age;
- duration of disorder;
- frequency of relapse;
- previous experience of medication;
- profile of side effect sensitivity;
- sex;
- state of fertility;
- risk to self;
- intensity of daily activities; and
- particular symptom profile.[7,9,12,13]


14. *Mezzich J E, Fabrega H, Coffman G A, "Multiaxial Characterisation of Depressive Patients",* J Nerv Ment Dis *(1987);175: pp. 339–346.*
15. *Tasman A, "Lost in the DSM-IV checklist: Empathy, meaning and the doctor-patient relationship",* Acad Psychiatry *(2002);26: pp. 38–44.*
16. *Lobo A, "On Multiaxial Psychiatric Diagnosis for General Medical Patients",* Br J Psychiatry *(1989);154(suppl. 4): pp. 38–41.*
17. *Verhoeven W M A, Tuinier S, "Two Steps Forward, One Step Back; Paradigmatic Changes in Psychiatry",* J Neural Transm *(2001);108: pp. 617–627.*
18. *Phelan M, McCrone P, "Effectiveness of Diagnosis Related Groups in Predicting Psychiatric Resource Utilisation in the UK",* Psychiatr Serv *(1995);46: pp. 547–549.*
19. *Mezzich J E, "Values and Comprehensive Diagnosis",* World Psychiatry *(2005);4: pp. 91–92.*
20. *Eager K, Gaines P, Burgess P et al., "Developing a New Zealand Casemix Classification for Mental Health Services",* World Psychiatry *(2004);3: pp. 172–177.*
21. *MaGPIe Research Group, "The Nature and Prevalence of Psychological Problems in New Zealand Primary Heatlhcare",* N Z Med J *(2003);116: p. 1,171.*
22. *Ashcraft M L F, Fries B E, Nerrenz D R et al., "A Psychiatric Patient Classification System: An Alternative to DRGs",* Med Care *(1989);27: pp. 543–557.*

These two areas thus reveal a wide range of clinical assessment-derived information that needs to be taken into account in developing a specific patient management plan.

This confirms that the end of the assessment process should firstly be a multi-axial classification. While the American Psychiatric Association's DSM for 25 years and the ICD-10 have chosen this approach, it can be seen from the above list that most of the axes currently used fall short of what is required for useful prediction.

It may be that some of the present axes have been demonstrated to be of questionable utility.[22–27] For example, the recording of physical disorders and life events in DSM-IV could be replaced by scales that record, in a standardised fashion, risk assessment, and/or by summarising the time course/chronicity of the disorder. Both of these approaches might make helpful contributions to clinical patient management plan development and set the stage for a changed axis one of DSM-IV to achieve a greater degree of complementarity between neuropsychopharmalogical developments and psychiatric classifications.

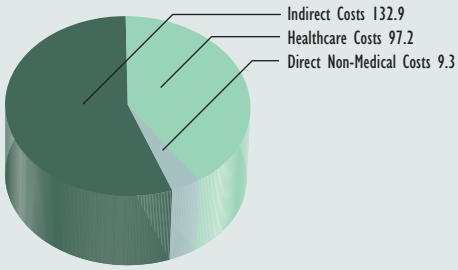
## Conclusion

The most promising way forward may be to link the above to the recognition that a valid classification in psychiatry may be more achievable by a dimensional approach.[2,28] If the research upon which the Clinical Practice Guidelines are based is valid, then recognising the underpinning neurophysiological dimensions and matching them with both pharmacotherapeutic agents and clinical phenomenology may prove to be a very manageable task. The depression/serotonergic and hallucinations/delusions/neuroleptic links may be a good starting point for thinking about two dimensions.

Acknowledging that the categorical approach that has gradually evolved from the contributions of Pinel and Kraeplin no longer needs to enslave researchers or clinicians may allow a more rapid and confident co-development of pharmaco-genetics and clinical therapeutics. ■

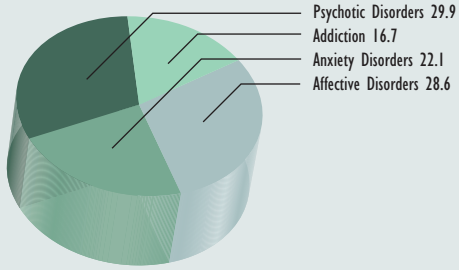

23. *Maricle R, Leung P, Bloom J D, "The Use of DSM-III Axis III in Recording Physical Illness in Psychiatric Patients",* Am J Psychiatry *(1987);144(11): pp. 1,484–1,486.*
24. *Skodol A E, "Axis IV: A Reliable and Valid Measure of Psychosocial Stressors?",* Compr Psychiatry *(1991);32(6): pp. 503–515.*
25. *Rey J M, Stewart G W, Plapp J M, Bashir M, Richards I, "DSM-III Axis IV Revisited",* Am J Psychiatry *(1988);145(3): pp. 286–292, (review).*
26. *Saavedra J E, Mezzich J E, Salloum I M, Kirisci L, "Predictive Validity of the Physical Disorders Axis of the DSM Multiaxial Diagnostic System",* J Nerv Ment Dis *(1997);189(7): pp. 435–441.*
27. *D'Ercole A, Skodol A E, Struening E, Curtis J, Millman J, "Diagnosis of Physical Illness in Psychiatric Patients Using Axis III and a Standardized Medical History",* Hosp Community Psychiatry *(1991);42: pp. 395–400.*
28. *Jablensky A, "The Nature of Psychiatric Classification: Issues Beyond ICD-10 and DSM-IV",* Aust N Z J Psychiatry *(1999);33: pp. 137–144.*


***Figure 1: Cost of Mental Disorders in Europe (2005) – Total = €239.5 billion***




*Andlin-Sobocki et al. studied the costs of different brain disorders in Europe and, as this figure shows, found that those costs could be divided into healthcare costs, direct non-medical costs and indirect costs. They estimated the total cost of mental disorders in Europe to €239.5 billion, of which €97.2 billion was healthcare costs.*

***Figure 2: Total Healthcare Cost of Mental Disorders in Europe By Category (2005) – Total = €97.2 billion***




*Looking more closely at the healthcare cost category, Andlin-Sobocki et al. found that it was topped by psychotic disorders (schizophrenia), followed by affective disorders (depression and bipolar disorder), anxiety disorders and addiction.*

*Source: Andlin-Sobocki P, Jönsson B, Wittchen H-U, Olesen J, "Cost of disorders of the brain in Europe",* Eur J Neurol *(2005);12(suppl. 1): pp. 1–27.*