Editorial

One Size Does Not Fit All: Observations on the "Phenomenon of Two-thirds" in Clinical Psychopharmacology

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Introduction

In clinical medicine the diagnosis is often established according to a known aetiology or an elucidated pathophysiology. A recent trend in management is to follow certain "evidence-based medicine" guidelines, which are often established by some consensus and then recommended as the "gold standard".[1] Psychiatric diagnoses, and the definition of a psychiatric disorder, are generally based on a cluster of symptoms or a syndrome, with a duration criterion as well. With advances in biological psychiatry, psychopharmacology and neuron-imaging, the pathophysiology of mental illness is often understood in terms of neuroanatomy, neuronal circuitry, neurotransmitters, and receptor systems.[2] Eisenberg[3] has succinctly summarised the aspirations of the biological school of psychiatry: "For every twisted thought there is a twisted molecule".

Certain symptoms tend to coexist in different illnesses. For example, a set of symptoms that reflects a diminution in mental and motor activity occurs in schizophrenia, affective disorders, basal ganglia diseases, and subcortical dementias.[4] However, no individual mental symptom is confined to a single disease, and virtually all the common symptoms of mental illness can occur in any of the currently recognised major mental illnesses.[4] Also, it is the norm that symptoms cluster in a similar manner in different diseases. Liddle[4] opined that this clustering reveals something of the inner structure of the human mind, and of the organisation of the supporting brain.

In psychopharmacology, a specific class of psychotropic drugs is developed for a specific category of mental disorder. However, the brain structures and their functioning maybe altered by the individual's psychic experience, physical needs, and environmental stimuli. As a rule, beneficial outcomes can be achieved only by simultaneously reducing symptoms and promoting the capacity of the individual to adapt to the exigencies of his or her life.[5]

The "Phenomenon of Two-thirds"

Interestingly, in clinical drug trials, the response rates of common mental disorders, such as anxiety, depression, and schizophrenia, to each drug within the specific psychotropic class investigated are about two-thirds (not excluding the placebo effect). The standard conclusion is that within each class of drugs, the efficacy for each disorder is about the same. This deduction implies that antipsychotic drug A is as effective as antipsychotic B in the treatment of schizophrenia, and that antidepressant X is as effective as antidepressant Y in the treatment of major depression. The main difference or selling point is thus in the side effect profile, severity of drug adverse reactions, or the speed of onset of action.

Brown and Khan[6] recently averred, 'Although antidepressants are clearly effective, when used in common practice their effectiveness is not astounding'. Even in patients who meet the criteria for a moderately severe depressive syndrome, the type considered most responsive to antidepressants, the improvement rate with antidepressant treatment is only about 70%. Furthermore, in these same patients the response rate to placebo is 30% to 40%.

Despite the two-thirds response phenomenon, diagnostic categories are becoming more differentiated, perhaps taking into account the multifactorial causes and varied manifestations. This might suggest specific nosological entities. By contrast, in recent years, psychopharmacotherapy has become *less* differentiated. Drugs which were registered originally for specific mental disorders are now promoted to treat other categories of mental disorder that may share similar symptoms. For instance, hallucination, delusion, disturbed behaviour or mood, and suicidal risk are common to schizophrenia, affective disorder, and the organic brain syndromes. This has occurred despite the exclusion criteria of other comorbid conditions or secondary symptoms. The "crossing over" of drug treatment is likely to be driven by the expiry of drug patents for a specific disorder, and by other market forces. Nevertheless, it means that psychiatrists need to review our diagnostic approach and the way clinical drug trials are conducted. The evidence on which drug treatment of psychiatric disease is based needs rigorous evaluation.

Limitations of Current Diagnostic Approach

It is generally agreed that the cause of mental disorder is multifactorial, spanning across the individual's physical, psychological, social and spiritual attributes and

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development. These attributes often interrelate, interact, integrate or disintegrate or dissociate continually from birth until the time of consultation. Mental disorder is present when there is abnormal subjective experience or anomalous behaviour observed, or both. The rapid advances in brain imaging have provided colourful and impressive results, but they do not explain fully the cause and effect, the mechanism, or the pathophysiology of mental disorders, which are too complex and dynamic to be pigeon-holed. The individual's mental functions and psychopathology are highly interrelated, interactive, integrated (or, conversely, disintegrated or dissociated), influencing both behaviour and the environment. In short, the whole personality is affected.

Diagnosis that is based on the nature and duration of symptoms is not the end-all, but only a part of the total assessment. A common pitfall of diagnostic systems is that diagnoses are portrayed as embodiments of real, discrete and unique entities. Therein lies the crux of the problem. Symptoms often have multiple origins and the clinician has to continually re-evaluate conventional boundaries and relations among diagnoses.[7] Though diagnoses provide practical aids to communication and prognosis, they inevitably oversimplify the patient's illness.

The Patients Involved in Drug Trials: One or Many?

Information in psychopharmacology is mainly derived from randomised, double-blind and placebo-controlled drug trials, which have been carried out based on diagnostic categories, using selected questionnaires and symptom rating scales. Colorado[8] highlighted the limitations of such information. Most of the "gold standard" (i.e., double-blind, placebo-controlled) studies are conducted in patients like those in primary care, rather than those seen by the psychiatrist. Patients with substance abuse and with comorbid psychiatric or medical conditions are often excluded from such studies. Antidepressant trials usually exclude patients with psychotic and bipolar depression and with significant suicide risk.

Industry-sponsored studies of mood-stabilising medications do not include those patients with complex mood cycling, commonly seen in specialty practice. The primary outcome variables are almost always changes in one, or at most a few, symptom rating-scale scores. The trial reports contain little discussion of the clinical importance of "statistically significant" changes, and no evaluation of changes in functioning.

In randomised controlled drug trials, individual patients are reduced to a consensus generic diagnosis and given a uniform regimen of drug treatment. This method may satisfy the scientific requirement of drug trials, but it distracts from proper holistic management of the individual. Psychosocial factors, cultural and environmental influences are often downplayed or totally ignored. So, the conventional drug trial may be inappropriate for evaluating treatment effectiveness in psychological illness.

It is often asked how each drug within the specific psychotropic class investigated (be it an antipsychotic, antidepressant, anxiolytic, anticonvulsant, or a mood stabiliser) differs from others in the same class. The better question to ask here is whether all patients suffering from the same illness (be it schizophrenia, depression, bipolar disorder, or anxiety disorder) are the same individuals, and in what ways they differ from one another.

An Evidence-based Approach to Psychiatry

In the past decade there has been a dramatic growth in evidence-based medicine, a natural development which attempts to link practice to research.[9] A multi-level guideline or algorithm of treatment was introduced, supposedly based on evidence from clinical research. In psychiatry, such guidelines aim at reducing or treating symptoms. They are really "one size fits all", a mono-dimensional guided trial-and-error system of management.

The fact that in clinical practice various classes of psychotropic drugs have been tried on different diagnostic categories with some efficacy implies a lack of specificity (i.e., a specific drug for a specific diagnosis). Thus, benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), beta-blockers, anticonvulsants, mood stabilisers, and conventional or atypical antipsychotics have all been trialled for anxiety disorders, mood disorders, and schizoaffective disorders with variable efficacy. The different drugs produce a similar "two-thirds response" (but not in the same two-thirds of patients for each drug). This is not surprising, as there is an interplay of multiple neuronal circuits in different regions of the brain, and various neurotransmitters and neuronal receptor systems are involved in each disorder. However, in holistic management, a thorough biopsychosocial evaluation and an understanding of the individual patient and his dominant symptoms help the prescriber to choose the specific drug most suitable for the person, and for the stage of the specific disorder

Indeed, the same argument may apply to electroconvulsive therapy (ECT), which is recommended mainly for severe depression, in particular with suicidal risk. However, in practice, ECT has been widely prescribed regardless of diagnosis, often for indications such as self-harm behaviour or threatened or actual violence towards others (unresponsive to antidepressant medication).

Towards Patient-focused Decisions and Individualised Treatments

Instead of treating all patients according to the clinical guideline of a specific diagnosis with a specific drug, adhering to a standard hierarchy of treatments, perhaps we

should focus on the individual patient and his or her biopsychosocial profile. It is just as important to know the patients and understand their problems, as it is to make a conventional diagnosis. Evidence informs practice, but it is not a substitute for patient-focused decisions that consider independent evidence of therapeutic value, personal choice, and the uniqueness of the individual.[10]

The choice of the first-line drug should be according to a patient's psychopathology or symptomatology, family and medical history, past response and affordability. When an effective drug has been chosen, its dosage should be titrated for the maximum relief of symptoms,with minimal side effects, and (ideally) no adverse reaction. Dosing and timing should take into consideration each patient's lifestyle and daily routine. Upon recovery and remission, the patient may be maintained on minimal medicines spread over a safe maximum period.

However, the patient should be protected with additional dosing against life events, stress, and situations of increased activity and arousal. Such anticipatory dosing should only be carried out if the patient's psychosocial circumstances, culture, and environmental factors are known. For instance, when there are pending stressful events (like festivals, school examinations, employment difficulties, financial hardship, or personal and family crises), suitable drugs ought to be advised to prevent a relapse. Even an interview, visiting a difficult relative, shopping in a crowded mall, or going on vacation may be stressful for some vulnerable patients.

Such patients may benefit from a cognitive-behavioural approach, or from an additional drug dose. Given that anxiety is the "mother of psychopathology", anxiolytics may ameliorate anxiety-symptoms associated with many psychiatric disorders. It is therefore unsurprising that these medicines are widely prescribed in primary care.

Although individuals after traumatic brain injury (TBI) may experience multiple concurrent neuropsychiatric symptoms, suggesting a single psychiatric diagnosis such as major depression, some of these symptoms may persist despite treatment of the apparent "diagnosis".[11] For this reason, the neuropsychiatric approach of evaluating and monitoring individual symptoms is necessary, and it differs from the syndromal approach of the conventional psychiatric paradigm. Several medications may be required to alleviate distinct symptoms after TBI. It is prudent to initiate the treatments one at a time to determine the efficacy and side effects of each drug.

We also suggest that clinical research and drug trials should focus on specific drugs for specific dominant symptoms (or symptom clusters), rather than for a specific diagnosis. Polypharmacy is not always inappropriate; sometimes 2 or more drugs are given for good pharmacological reasons. There may be synergistic effects for agents with different pharmcological actions. Anecdotally, a combination of trifluoperazine (perhaps other antipsychotics too) and an SSRI (e.g., fluvoxamine) might be more effective for persistent auditory hallucination than an antipsychotic alone. Amisulpride (perhaps combined with a SSRI, eg escitalopram) might be more effective for delusions in the elderly. The hypothesis is that these psychotic symptoms have an underlying recurrent thought, akin to obsessional rumination. Where the caregivers show high expressed emotions (EE), tianeptine, acting through the hypothalamic-pituitary- axis, may prevent a relapse in schizophrenia and depressive illness, especially when the patient has added stress.

Conclusion

In clinical psychiatry, accurate diagnosis and classification may provide some clues for developing psychopharmacological strategies. However, the clinician should not expect to find a close correlation between the types of patients encountered in practice and the classic prototypes studied in drug trials. This caveat may prove particularly relevant when the clinician follows a patient over months or years. A flexible approach is needed – one that includes routine and regular reassessment of the patient's condition, life circumstances, and consideration of the need for changes in medications and other interventions.[5] Polypharmacy may be inevitable when psychiatric symptoms are dynamic. Diagnostic parsimony should be sought, but it may not always be the best ldiagnostic approach in many clinical populations.

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