Editorial

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Psychopharmacological Practice: The DSM Versus The Brain

Thomas L. Schwartz*

ABSTRACT

In 1952, the Diagnostic and Statistical Manual of Mental Disorders (DSM) system of creating, validating, studying and employing a diagnostic system in clinical psychiatric practice was introduced. There have been several updates and revisions to this manual and, regardless of its a theoretical framework, it actually does have a framework and presupposition. Essentially the DSM dictates that all psychiatric disorders are syndromes, or a collection of symptoms that commonly occur together and impair psychosocial functioning. These syndromes allow for homogenous groups of patients to be studied and psychotherapies and pharmacotherapies to be developed. This editorial will examine the DSM system with regards to its applicability to central nervous system dysfunction where psychiatric disorders are concerned. Specifically, the brain does not follow categorical, or syndromal, constructs. In fact, the psychiatric patient likely inherits several risk genes that promote abnormal proteins along several neuropathways in the brain. These abnormalities create dysfunctional neurocircuits which create individual psychiatric symptoms, but not a categorical syndrome or diagnosis. The concept that the DSM may be excellent for clinical diagnostic purposes, but less correct in its assumptions for a psychopharmacologist's treatment approaches will be discussed.

**M.D. Associate Professor, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY, USA. Tele: 315 - 464 - 3100. Fax: 315 - 464 - 3163.*

Address correspondence to: Dr. Thomas L. Schwartz, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY, USA. Tele: 315 - 464 - 3100. Fax: 315 - 464 - 3163. E-mail: schwartt@upstate.edu

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Introduction

This paper was initially to be titled, 'The Fundamental Presuppositions Of Psychopharmacology,' but with the advent and likely introduction of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 by the American Psychiatric Association (APA, In Press[2]), it seemed more timely to initiate a discussion for the future prescriber regarding how the DSM system currently drives the utilisation of psychopharmacology, its merits and pitfalls.

Essentials of the Diagnostic and Statistical Manual of Mental Disorders [DSM]

Essentially, if a psychiatric disorder appears in the DSM, it likely has a medication management option as a gold standard, if not its first-line treatment. The way a disorder is defined in the DSM sets up how the illness is studied and how medications can ultimately be approved for use. The DSM presupposition might be that if a psychiatric disorder is deemed to exist, then it can be studied using a more accurate diagnostic process, and the likelihood of finding a psychopharmacologic treatment is elevated. In this manner, a way of classifying psychiatric syndromes drives the exploration for treatment and ultimately disease management via medications or psychopharmacology. Therefore, clinicians prescribe based upon a patient's diagnosis. This method of *diagnosis driving treatment* is similar to other specialties (general medicine, neurology, paediatrics, etc.) and their approach to medical care.

This approach makes intuitive sense if one can homogenise a population of people suffering from a psychiatric disorder, enrol them into a study and give them a certain dose of medication. This assumes that each schizophrenic, or each depressive, is identical in symptoms, psychology, social connectedness and underlying biological brain functioning.

In fact, clinicians know that each patient is inherently different. Each individual patient must have his or her illness treated differently when compared to others, and often times in a unique manner. For example, one patient may respond to risperidone and a second fails this drug and requires iloperidone. One patient may develop side effects that are intolerable on paliperidone, whereas another patient has full remitted symptoms on the same drug without any side effects. It is possible that a patient has his or her depression fully alleviated except for ongoing insomnia after taking a selective serotonin reuptake inhibitor (SSRI).

This person may need a hypnotic agent such as zaleplon, whereas another similar patient, albeit with an addiction history, may require ramalteon. The DSM-based model assumes all patients are equal and homogenous. It fails to address this reality clinician's experience in direct patient care where most psychiatric patients are symptomatically heterogeneous.

Even if this were so, with the DSM diagnosis driven scientific method, researchers can repeat studies and validate findings. Next, a regulatory agency, i.e., Food and Drug Administration (FDA), can allow widespread psychotropic prescribing to a theoretically similar, but likely very individualistic, patient in the general population. Using this model, clinicians should expect to obtain similar results in their patients.

Taking major depressive disorder as an example

Using major depressive disorder (MDD) as a working example, now and throughout this paper, consider if a certain percentage of patients always achieve antidepressant response on an SSRI in studies. If so, clinicians should expect these outcomes in their real-world patients every time. To bring this up to the present day, the latest approved antidepressant, vilazodone, appears to have more serotonergic facilitation than the most commonly prescribed SSRIs, and has similar outcomes as well (Schwartz and Stahl, 2011[18]). For example, MDD patients who take 40 mg/d can expect a 40% chance of gaining a 50% symptom reduction (Rickel *et al*., 2009[15]) or greater. This would suggest that a sizeable minority of patients should get better following a single monotherapy. The US government funded STAR*D (Sequenced Treatment Alternatives to Relieve Depression)[29] trial would suggest, however, that the average MDD patient might respond to an initial SSRI at a rate of 47% (Sussman, 2007[30]), which is comparable to the pharmaceutical company funded vilazodone trial above. Non-responders in STAR*D continued to be enrolled and were allowed to be successively treated with increasingly complex medication regimens and combinations, i.e., lithium augmentation, monoamine oxidase inhibitor (MAOi) monotherapy, venlafaxine ER plus mirtazapine, etc., Over four arms of successive treatment options, about 70% of patients had their depressive symptoms lowered remarkably. Therefore, there exists conflicting evidence that simply making a validated diagnosis, i.e., via the DSM, will equal a satisfactory clinical outcome. STAR*D would suggest that despite aggressive treatment with several medications, there are still 30% of MDD patients that clinicians fail to fully treat to wellness.

Furthermore, when large groups of psychopharmacologists are polled, how often do they say they achieve these validated, official monotherapy outcomes that are based upon initial DSM diagnoses? If it was 100%, then clinicians should expect that the first and second SSRIs introduced (fluoxetine/sertraline) should have treated 50%–60% of the world's MDD patients. Clearly, 60% of the world's depression has not been treated by using a diagnosis-based model to drive psychopharmacology practice. This method has failed to yield

remarkable results. As noted, STAR*D suggested that it often takes several, clinically aggressive, rating scale driven medication attempts to successfully treat MDD to remission. Outside of sequential monotherapy trials, a *typical* psychopharmacologist, treating a *typical* caseload of depressed patients, will state that monotherapy approaches are actually uncommon, and polypharmacy practices are the norm (Schwartz and Rashid, 2007[17]). The average prescriber writes his MDD patients two or three medications each. Furthermore, MDD is being classified as treatment resistent more often where patients have been found not to respond to an initial treatment. MDD is chronic and recurrent in 60% and 40% of patients, respectively (Greden, 2009[8]; Kessler *et al*., 2003[9]; Keller and Boland 1998[10]; Keller and Shapiro, 1982[11]; Mueller and Leon, 1996[13]; Fava *et al*., 2003[6]) and MDD is considered the most disabling condition worldwide and the fourth greatest contributor to global health burden (World Health Report. Message from the Director-General, 2001[31]).

Given the increasing prevalance, disability, recurrence and chronicity noted above for MDD, clinicians, researchers, educators and theorists must now revisit the idea that a distinct diagnosis should drive a single monotherapy treatment. The outcomes for schizophrenia and bipolar disorder are likely even less favourable using the presupposition that diagnoses should drive psychopharmacological practices. This categorical model will work for a solid minority of patients, but often times does not for the remaining treatment-resistant patients. This approach often leaves patients only partially treated, with residual symptoms and greater risk of relapse and chronicity. A monotherapy, one-drug-fits-one diagnosis approach, is likely to never exist.

Why is this the case?

Working with and validating a DSM-based diagnosis entails a lot of field work, clinical debate and statistical analysis (Regier *et al*., 2009[14]). The DSM system expects that each clinical diagnosis or syndrome should ultimately be validated by its separation from other disorders, common clinical course, genetic aggregation in families, and further, differentiation by future laboratory tests (including anatomical and functional imaging, molecular genetics, pathophysiological variations and neuropsychological testing). Differential response to prospective treatments (pharmacotherapy and/or psychotherapy) may also be utilised to differentiate psychiatric disorders. Through the years of the evolution of the DSM system, diagnostic criteria have been tested in multiple epidemiological, clinical and genetic studies, and sometimes clear separation of these syndromes is less apparent due to the high levels of comorbidity that are often reported within each patient. In addition, treatment responses are now less specific as some medication pharmacologic families, i.e., SSRIs, selective serotonin-norepinephrine reuptake inhibitors (SNRI), second-generation antipsychotics (SGA), are often found to be effective for a wide range of anxiety, mood, and eating disorders. As an example, atypical antipsychotics

have received indications for schizophrenia, bipolar mania or depression, treatment-resistant MDD, and aggression in autism (Kim *et al*., 2009[12]). SSRI and SNRI antidepressants are also available to treat depression, eating disorders, premenstrual disorders, pain and anxiety disorders (Stahl, In Press[22]). The DSM-V founders, in fact, assigned a study group to look past the usual *categorical* diagnostic structure in order to investigate *spectrums* of disorders to better accommodate this idea that some symptoms cross over between diagnoses as do many comorbidities travel together when diagnosing psychiatric patients. The DSM-V will retain much of its categorical, diagnosis-specific language, but seems likely to be poised to start addressing dimensional overlap and evaluation of certain symptoms, or clusters of symptoms within each diagnosis. This may fit better with the way the brain's neurocircuitry actually works. For example, with regard to schizophrenia, rather than viewing it as a disease entity represented by psychosis, the construct will be deconstructed into component psychopathology domains and each domain will represent a clinical target for aetiologic and therapeutic discovery (Carpenter, 2012[4]).

The problem with DSM

Either way, the DSM is a great system for taxonomy that allows for enhanced clinician communication about disease states and allows for a great deal of research-based activity. However, as in the example of MDD above, this method does not translate into viable treatment monotherapy options. It is seemingly naïve, as in the case of SSRI antidepressants, that simply elevating serotonin levels in the central nervous system (CNS) will treat all nine defined MDD symptoms of the DSM. Is the brain controlled by one neurtransmitter, or hundreds? The presupposition would be that all MDD patients suffer from serotonin deficiency and all nine MDD symptoms are each caused by this deficiency as well. Therefore, using an SSRI and elevating serotonin should alleviate depression worldwide. Again, this has not happened. The presupposition that a 'diagnosis' should drive a clinician's prescribing seems awry.

The problem lies in the fact that a psychiatric diagnosis is a syndrome. A syndrome is a collection of individual symptoms that often accompany each other and aid in making a uniform diagnosis. The DSM diagnosis appears to be dictating what symptoms should exist, instead of the symptoms that the patient suffers from driving the actual treatment or treaments. A clinician should treat the individual patient, first by applying good descriptive (DSM) diagnostic measures and then specifically addressing each specific, individual symptom that the patient is uniquely suffering from.

Why is this important? Did the brain evolve around the DSM and this diagnostic system? Can a whole psychiatric disorder be traced to one brain area? The answer is no; however, specific symptoms may be mapped to specific brain areas or neurocircuits often theoretically, and on occasion, more factually.

In this manner, several different parts of the brain may be malfunctioning, thus causing several symptoms to develop. Once enough symptoms develop, a syndrome or diagnosis is formed or created, and *now* the DSM makes sense. Basically, symptoms drive the disorder and diagnosis. Symptoms come from dysfunction of certain brain areas and psychiatric prescribing likely should be based upon each individual symptom experienced by the patient.

The point may be raised here: This would amount to mere symptomatic treatment, which is anathema to diagnostic formulation and management. Isn't diagnostic management the basis of medical treatment, and symptomatic treatment to be frowned upon? Isn't that one of clinical medicine's basic tenets?

I think the basis of making a diagnosis is to collect symptoms until they equal a defined syndrome and this equals a 'diagnosis.' This is how the DSM does work. This is how medicine works. The thesis of this paper is that making a syndromal diagnosis (a collection of symptoms) is fine; but for psychiatric disorders, clinicians really need to look at each symptom specifically as each symptom arises from different brain constructs or circuitry. I am not discarding syndromal categorical diagnoses, but suggesting that prescribers look more precisely at each symptom, and use neurogenetics and neuroimaging to pick better treatments.

A medication may be able to remedy a dysfunctional brain circuit, or circuits, and individual symptoms would then diminish. This should be a modern presupposition for psychopharmacological prescribing. First, identify the symptom. Second, identify the brain area that is faulty and promoting the symptom that is causing suffering. Research, develop and prescribe a drug that can treat the brain's defective circuits and ultimately relieve one individual symptom at a time.

Individual medications for individual symptoms

The concept of using individual medications to treat individual symptoms of a disease is not uncommon in medicine. Take for example, a female patient in menopause who is treated with oestrogen replacement, but continues with vasomotor hot flashes, vaginal dryness, and develops osteoporosis. She might be given, in addition to oestrogen, an SNRI antidepressant to treat vasomotor symptoms, an oestrogen vaginal cream for dryness and a bisphosphonate for bone loss. Using this medical model approach would be supported by way of rational polypharmacy and tailoring treatment to each of the patient's specific MDD symptoms in a similar manner.

An MDD patient may need three medications to treat the nine DSM symptoms (the syndrome or diagnosis) to promote full remission because his/her MDD is caused by more than just a serotonin circuitry deficiency.

Borrowing from Stahl's work entitled 'From Circuits to Symptoms' (Stahl, 2003[23]), this idea that dysfunctional brain circuits can produce psychiatric symptoms can be further elaborated. Separate and distinct neuranatomic brain areas are connected by neurons (Stahl, 2003[23]). The neurons and brain areas are linked together by neurotransmitters, their receptors, and the enzymes that build up and destroy these transmitters. If a patient inherits genes from his or her parents that code for defective proteins (receptors, enzymes, etc.), then these proteins might change the firing or functioning of specific brain areas. This dysfunction may cause individual MDD symptoms to emerge as an example.

Phenotype, genotype and endophenotype

Another way to explain this would be to discuss the difference between a phenotype, genotype and endophenotype. Imagine that a patient came to the office and agreed to obtain a cheek swab for DNA genotyping. These genes were inherited by both parents and code for both normal and abnormal proteins which may convey risk or protection regarding a myriad of medical disorders, i.e., diabetes, breast cancer, MDD, schizophrenia, etc.

A person's genes make up a genetic code or *genotype*. Some genes may be turned on, or off, during the course of the patient's life. For type II diabetes, genes may turn on for insulin receptor insensitivity, and this genotype may allow for glucosaemia which leads to polydipsia and polyurea. These latter two symptoms are now noticed by the patient as they are external. His, or her, outward appearance, signs or symptoms now become his or her *phenotype*. A parallel model with depression might include normal patient functioning followed by the onset of a dysphoric mood and poor concentration as hallmark depression symptoms. This patient obviously has genes and a genotype, where over time genes are activated, or inactivated, and the MDD symptoms (phenotype) emerge.

Psychiatric symptoms are sometimes hard to detect and even harder to measure. Bloodwork cannot be drawn to detect the level of dysphoria like a blood glucose could be drawn in the diabetic; so, psychiatry continues to look for biomarkers, or ways to detect symptoms early to treat disorders early, aid in diagnosis, or better, delineate one disorder from the next. Use of functional neuroimaging may provide this type of detection. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are two such techniques. By case–control imaging between MDD and normal subjects, researchers may identify parts of the brain that are hyperactive or hypoactive compared to normal controls. These findings are *endophenotypes*. For example, the dorsolateral prefrontal cortex (DLPFC) in MDD may be hypoactive and lead to the symptom of poor concentration. This may be detected on fMRI scans. Therefore, the MDD patient has a *genotype* consisting of MDD risk genes and, when activated, the fMRI might reveal DLPFC hypoactivity (*endophenotype*), and poor concentration (*phenotype*) emerges as a symptom (Stahl, 2003[24]).

The psychopharmacologist of the future might use the syndromal DSM approach (phenotype) and choose sequential monotherapies. Again, using MDD as an example, he or she would have the option also to:

- Obtain a cheek swab (genotype) for each MDD patient;
- Obtain a functional brain scan (endophenotype); and
- Choose a monotherapy or polypharmacy approach based upon pharmacogenomics or neuropharmacoimaging, and statistically choose a regimen that is more likely to be effective and tolerated, rather that running through one US FDA approved monotherapy at a time based upon intuition and the presupposition that all antidepressants are equal in efficacy (Stahl, 2010a[20]; Filakovic and Petek, 2009[7]; Stahl, 2010b[21]).

Genotype–endophenotype–phenotype target symptom-based approach

The next section of this paper will present a case for discussion where the future psychopharmacologist utilises a *genotype–endophenotype–phenotype* target symptom based approach.

Case

The patient is a 50-year-old man who is presently admitted to psychiatric hospital because of severe MDD. He has suffered from MDD symptoms for 10 months consecutively with symptoms progressing from mild to incapacitating. He admits to having impaired concentration, marked fatigue, depressed mood with suicidal thoughts, insomnia, ruminations of worthlessness, and feelings of guilt. This is his first diagnosed depressive episode and he has had no drug treatment prior to this hospitalisation. He likely suffered from dysthymic disorder throughout his adult life. He is amicably separated and has three grown children who are doing well. His biological family suggests ADHD symptoms in a nephew and schizophrenia in an elderly uncle. He drinks alcohol occasionally, but there is no indication of misuse. He has mild obesity, and environmental allergies, but is otherwise healthy.

Commentary

According to most treatment guidelines, this patient could be given any first-line antidepressant without much guidance as he is in his first episode and has no apparent outward phenotypic family history of depression to guide treatment. Most psychopharmacologists would choose a simpler agent such as an SSRI and begin treatment based upon their comfort level for the particular SSRI chosen.

A psychopharmacologist in the future may be able to use the *genotype–endophenotype–phenotype* approach by gathering a cheek swab and sending away the patient's genetic material for a genotype analysis. In this case, some hypothetical findings may occur:

Genotype

The patient has (1) 'short' s/s alleles for the *SLC6A4* gene which codes for the serotonin transporter (reuptake pump) protein, (2) Ins/Ins alleles for the *DRD2* gene that codes for the dopamine-2 receptor, (3) the COMT gene alleles of 158 Val/Val, 472 G/G, (4) *CACNA1C* gene's G/G alleles which modulate calcium channels in the glutamate neuropathways; and (5) *MTHFR* gene alleles of T/C which governs metabolism of folate and the ability to generate monoamines.

Endophenotype

Next, the patient undergoes an fMRI brain scan with several prominent findings. First, it is noticed that the DLPFC is hypoactive compared to control (non-MDD) patients during executive functioning stressor conditions, as seen theoretically in Figure 1. Second, there seems to be hypoactivity in linking the connectivity between the DLPFC and the anterior cingulate cortex (ACC) (Aizenstein *et al*., 2009[1]).

The hypothetical image in Figure 1 is adapted from Aizenstein *et al*., (2009[1]) suggesting that this MDD patient has underactive and less neuronal firing in both DLPFC areas, compared to normal, non-depressed controls.

Also, a whole-brain, resting-state fMRI connectivity multivariate analysis suggested a pattern consistent with MDD diagnostically and shows hyperactivity in the amygdala, ACC, parahippocampal gyrus and hippocampal areas, as suggested in Figure 2.

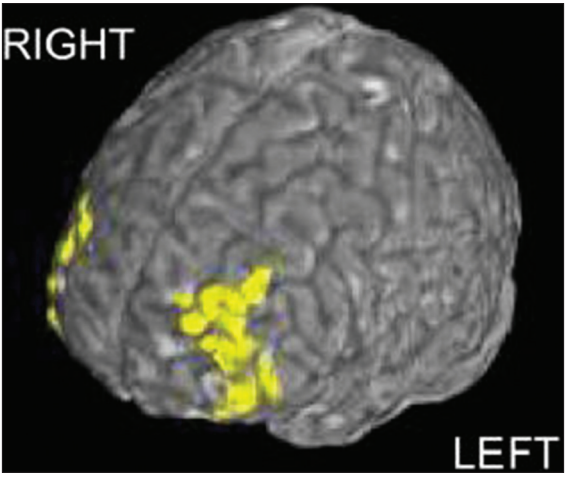

Figure 1: Hypofunctioning of the dorsolateral prefrontal cortex in major depressive disorder. (From Aizenstein *et al*., 2009[1]. *Reproduced with permission obtained by author.)*

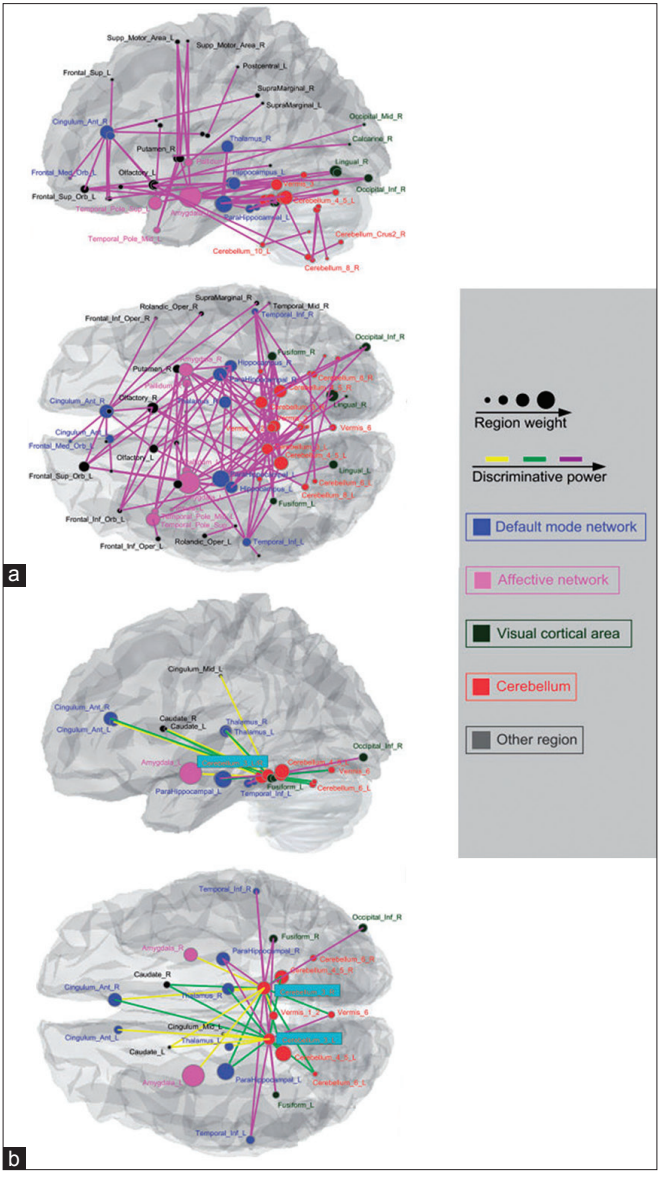

Figure 2: Neurocircuitry in major depressive disorder (MDD): In this figure, complex analyses based upon functional neuroimaging can determine not only which specific neuroanatomic areas are hyper or hypofunctional in the MDD patient, but further analyses the strength, or weakness, in the connectivity between brain regions. This may help delineate MDD from control subjects and possibly determine which brain endophenotypic findings need to be remedied to alleviate symptoms (Zeng *et al.*, 2012.[32] *Reproduced with permission obtained by author.)*

Guided genotype–endophenotype–phenotype approach

If the above *genotype–endophenotype–phenotype* information was available and validated in widespread fashion, and within the armamentarium of the psychopharmacologist's clinical practice, how might these findings aid in treating the patient with MDD?

Again, MDD treatment guidelines might suggest choosing any available first-line antidepressant. But with knowledge of the genotypic findings, an astute psychopharmacologist would consider the following for this case:

Genotype

For the SLC6A4 serotonin transporter gene, this patient is homozygous (i.e., has two copies) for s/s alleles which may indicate individuals who are more likely to exhibit poor responses to SSRI treatment or develop more adverse effects from SSRI use. For the C*OMT*, 158 Val > Met (472 G > A, rs4680) genes, he is homozygous for (158 Val/Val, 472 G/G) which may indicate MDD patients who are more likely to suffer from cognitive and executive dysfunction symptoms. The patient is (G/G) homozygous for the *CACNA1C*, G > A rs1006737 gene. The G alleles tend to be protective against future MDD relapses and may allow for greater remission maintenance after successful treatment. The dopamine-2 receptor gene, *DRD2*, shows that this patient is homozygous for (Ins/Ins) and likely indicates that this patient may benefit from augmentation with an atypical antipsychotic. Finally, he is heterozygous for T/C alleles for the *MTHFR* (folate) gene. His present T allele may indicate that he is more likely to experience associated cognitive, executive functioning symptoms, especially as he also expressed the Val variant of the *COMT* gene.

Knowing these findings, a psychopharmacologist might choose not to prescribe an SSRI as its likelihood of being effective is low and side effects will likely mount. This patient does have significant ruminative and suicidal symptoms, which are often felt to be driven by the serotonin pathways in the CNS. If these pathways need to be manipulated, then choosing a psychotropic with known ability to manipulate serotonin activity outside of the SSRI or SNRI class is likely warranted. Agents such as mirtazapine, trazodone, or an MAOi might be chosen as they do not rely heavily, or at all, upon serotonin reuptake inhibition (e.g. mirtazapine has no SRI, trazodone is weak, even MAOis have no SRI component). This approach might statistically improve the patient's chances of achieving remission with a minimum of monotherapy trials. In other words, a genotypic approach may improve the chances of prescribing the best psychotropic first as tailored to the patient at hand.

Endophenotype

The functional neuroimaging endophenotype approach would support the contention that the patient has a risk-laden genotype for depression

and suicidality, given that limbic structures such as the amygdala are hyperfunctioning and overactive. His genotype would suggest that he is at risk for experiencing poor concentration, fatigue and executive dysfunction, which is supported by the imaging findings of a hypoactive DLPFC.

Focussing now on the underfunctioning DLPFC and his vegetative MDD symptoms, the psychopharmacologist should choose agents that are more likely to activate and facilitate improved functioning of the DLPFC (Stahl *et al*., 2003[25]). For example, improving dopamine, norepinephrine or histamine activity in the DLPFC may preferentially improve this endophenotype and increase DLPFC neuronal firings. Drugs that may improve his MDD symptoms would include those with primarily norepinephrine reuptake inhibition: Tricyclic antidepressants (TCA) like desipramine, protriptyline, nortriptyline or the novel antidepressant bupropion. Use of an MAOi would also elevate norepinephrine and dopamine in the cortex. Histamine may be facilitated by modafinil or its isomer armodafinil (Stahl, 2011[27]).

Theoretically, the MDD patient presented in the case above could be started early on with an MAOi, covering his genotypic and endophenotypic findings and risks. This would raise all three monoamines at the onset and avoid the fruitless use of an SSRI or SNRI initially. Instead of using an MAOi as the 5th or 6th treatment, it could be utilised earlier in care, despite its drug interaction or hypertension risks, as there might be evidence to suggest it would have a greater chance of working with greater tolerability initially when compared to the SSRI or SNRI class. Realistically, choosing a serotonergic agent such as mirtazapine might be warranted as it could facilitate both serotonin and norepinephrine easily. Addition of a more noradrenergic agent such as desipramine at, or near, the onset of treatment would further optimise this patient's suffering neurocircuits. In fact, there are some combination initiation treatments that favour simultaneous starting of two antidepressants at once, such as mirtazapine plus an SSRI, SNRI, *NDRI*, TCA, etc.; and they have been shown to be clinically and statistically effective in MDD (Stahl, 2010[28]; Blier *et al*., 2010[3]). This guided *genotype–endophenotype* polypharmacy approach may be able to facilitate serotonergic activity in the limbic system (Carter and Krug, 2009[5]) and noradrenergic activity in the DLPFC (Stahl *et al*., 2003[25]; Schwartz and Nihalani, 2011[19]) that specifically addresses this patient's individual MDD symptoms.

In conclusion, pharmacogenetic studies plus functional neuroimaging studies suggest that for each patient, certain brain areas are in need of functional amelioration and may be more likely to respond to the multiple pharmacodynamic properties of the antidepressants being combined at initiation of treatment. A broad, categorical, and unidimensional approach by the DSM to psychiatric disorder likely does a disservice to individual, heterogeneous patients with wide differences who are being treating in the office-based setting.

A genotype–endophenotype, phenotype approach might allow faster, safer individual patient-based care in the future.

It may be said that emphasis on genotypes and mutations in the present text ignores the apparently vast contribution of epigenetic modifications, of gene–gene and gene–environment interactions. This is no doubt important, but more complex and either out of the scope of this paper or would make it too lengthy. If *MSM* wants a paper about this very important area down the road, then let us commission it.

Concluding Remarks [See also Figure 3]

The categorical approach to psychiatric diagnosis employed by the DSM series is worthwhile and even invaluable. It allows clinicians to speak a common language, educate their patients and utilise research diagnostic validated principles in regards to drug development and best practices for psychiatric treatment. Almost every psychopharmacology textbook discusses the DSM system and the treatment guidelines that are derived based upon using DSM diagnoses.

However, the brain likely did not evolve secondary to the DSM system and does not act in a categorical fashion. This paper, by using MDD as an

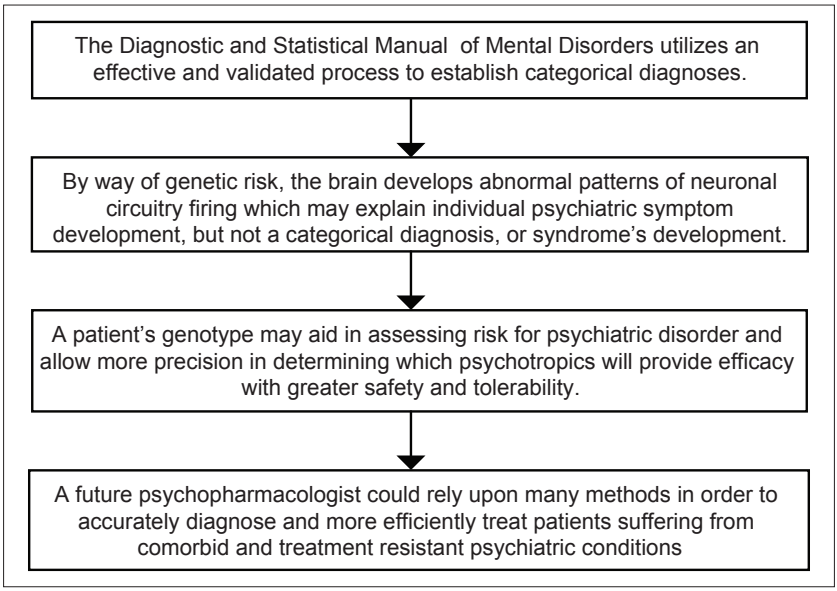

Figure 3: Flowchart of paper

example, has attempted to show the reader that psychiatric patients all inherit subtle molecular vulnerabilities [genotypic mutations that yield risk for individual symptom development, not whole syndrome development (Stahl, 2007[26])]. If enough mutations occur in specific neural pathways, then certain brain areas and their connections may become dysfunctional (hypoactive or hyperactive compared to controls) and possibly endophentypically detectable upon functional imaging. A gifted, or hard working, academically minded psychopharmacologist might be able to utilise genotypic and endophenotypic findings to dictate initial psychopharmacological regimens and management to more directly target these defective neuropathways, and bring about a normalisation of the endophenotypic findings and facilitate symptom resolution. This 'circuits driving symptoms' theoretical approach may actually mimic brain function moreso than the DSM-validated syndromal diagnostic approach.

Take home message

1. Utilise sound psychiatric interviewing and diagnostic approaches. Use of the DSM system is validated and makes intuitive syndromal and clinical sense.
2. Aggressive use of psychotropic monotherapy is warranted for mild to moderate levels of psychopathology. As symptom severity, complexity, comorbidity or resistance increases, the presuppositions of the DSM model fail in clinical practice as CNS functioning involves genotype–endophenotype–phenotype symptom development.
3. In the future, these resistant, or refractory, cases may be better served by using pharmacogenomic and functional neuroimaging approaches to detect malfunctioning neurocircuits and choosing the most statistically, and likely, effective psychotropic(s) earlier in treatment.
4. Until this type of standardised treatment approach is validated, psychopharmacologists should continue to use rational polypharmacy (Schwartz, 2010[16]) based upon knowledge of the likely affected neuroanatomic areas, their connnectivities, and which pharmacological agents may target those areas in order to mitigate specific psychiatric symptoms.

Conflicts of interest

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Declaration

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Questions that this Paper Raises

1. Does the DSM system make intuitive sense in regards to categorical psychiatric diagnostic practices?

2. Does the DSM system make neuroscientific sense in regards to categorical psychiatric diagnostic practices?

3. What might a psychopharmacologist do to achieve better patient outcomes in the future?

4. Might treatment be personalised based upon genetic testing or functional neuroimaging?

5. Polypharmacy and off-label prescribing are common in psychopharmacology practice. In the absence of a robust evidence base, how can these practices be justified theoretically?

6. How might these practices be studied and validated in the future?

About the Author

Thomas L. Schwartz, MD, received his medical degree from and completed his residency in Adult Psychiatry at the State University of New York (SUNY) Upstate Medical University in Syracuse, New York. Dr Schwartz is currently Associate Professor of Psychiatry, Director of Adult Clinical Services, and Director for psychiatric undergraduate medical student training at SUNY Upstate Medical University, where he also directs the Depression and Anxiety Disorders Research Program. Active on many committees at SUNY, he also provides direct resident supervision, lectures in several courses, and directs and organises continuing medical education events for the psychiatry department. Dr. Schwartz also maintains a private practice and consultation practice. He is a member of the American Psychiatric Association and has been honoured with their Nancy Roeske, MD, and Irma Bland Certificates of Recognition for Excellence in Medical Student and Resident Education from the American Psychiatric Association. Dr. Schwarz has served as principle investigator on many clinical trials; his clinical and research interests include treatment-resistant depression and anxiety, psychosomatic illness, adult psychopharmacology, and antidepressant augmentation for efficacy and tolerability. He is the editor of Depression: Treatment Strategies and Management, 2nd Ed. Informa (2009).