Taking the depressed "person" into account before moving into personalized or precision medicine

Clinicians and patients suffering from major depression are confronted with the gap between guidelines produced by so-called evidence-based medicine and prescription patterns emerging from experience-based medicine, as well as with the gap between artisanal prescribing and the siren song of personalization, stratification and precision medicine.

Perlis' elegant paper describes the many challenges in abandoning personalization to get to precision in the pharmacotherapy of depression[1]. Currently, physicians indeed practice some form of personalization by taking into account the patient's symptom profile as well as the safety and tolerability of the different antidepressants, although taking the symptom profile into account is not or poorly empirically supported. Actually, the choice of a specific antidepressant is mainly based on the presence of a specific symptom (52%) or the wish to avoid a specific side effect (49%), and the specific symptoms considered are mainly anxiety (20%), insomnia (18%) and fatigue (14%)[2].

Before antidepressant treatment can start moving from artisanal prescribing to precision medicine, several issues should be addressed. Taking more into account the "anima" (the individual, the real person, as well as the illness) and not only the "persona" (mask, character imposed by our diagnostic and assessment tools) seems to be mandatory.

That randomized clinical trials (RCTs) really represent the gold standard is questionable: "never before have the inadequacies of RCTs been so apparent to so many; yet, equally, never before have those in position of authority – from regulators, to policy-makers, to doctors – relied so extensively on RCTs' evidence"[3]. Efficacy estimates are usually based upon RCTs, but only about 10 to 20% of daily practice patients "fit into" exclusion and inclusion criteria.

Furthermore, efficacy estimates taken from RCTs heavily depend on study design: response rates of 52% and 34% for antidepressant and placebo, respectively, in two-arm studies, 58% and 45% in three-arm studies (two antidepressant arms, one placebo arm) and 65% in studies comparing two antidepressants; these differences can only be explained by the changing probability of receiving placebo: 50%, 33% and 0%, respectively[4].

The role of patients' expectations was also shown by a trial comparing sertraline, hypericum and placebo, which found no effect of assigned treatment on clinical improvement, but a significant effect of patient's guess on which treatment he/she was assigned to: patients who guessed taking sertraline or hypericum had significantly higher response rates (56% and 68%, respectively) than patients who guessed taking placebo (24%)[5].

Many patients have ambivalent attitudes towards antidepressants that significantly influence outcome: patients with a rather negative, neutral or rather positive attitude towards taking antidepressants at baseline were found to have placebo response rates of 34%, 36% and 56%, respectively, and antidepressant response rates of 51%, 56% and 69%, respectively[6].

Socio-demographic characteristics are seldom taken into account, but variables such as living with other persons (versus living alone) or being unemployed (versus employed) dramatically influence the outcome of antidepressant treatment (OR: 2.81 and 0.27, respectively)[7]. There is also an ongoing debate on whether taking into account the patient's preference for pharmacotherapy or psychotherapy influences outcome. All these aspects should be considered before we try to improve our treatments for depression, be it by personalization, stratification or precision medicine.

In addition, the "persona" of the diagnostic criteria and of the assessment tools only partially represents the "anima" of the patient and of the depressive illness. A major depressive episode cannot be fully understood either by nine DSM or ten ICD criteria, or by ten Montgomery-Åsberg Depression Rating Scale (MADRS), seventeen Hamilton Depression Rating Scale (HAMD) or thirty Inventory of Depressive Symptomatology (IDS) items.

One important limitation of the DSM criteria for major depressive episode is the massive heterogeneity they cause: almost endless combinations of criteria are possible. Indeed, when you need five out of nine criteria and, moreover, most of these criteria are compound (e.g., psychomotor retardation or agitation), two patients with major depressive episode can have no symptom in common. This of course hampers "personalized" treatment as well as clinical and etiopathogenetic research.

When assessing change during treatment, the standard rating scales face the same problems. Moreover, the HAMD covers a lot of associated anxiety and neurovegetative symptoms, while the IDS has a 16-item version closely reflecting the DSM criteria and a 30-item version adding commonly associated symptoms (anxiety, irritability) and items relevant to depression "subtypes". DSM depression symptoms (included in the IDS 16-item version) do not seem to be of higher clinical relevance than non-DSM symptoms (additionally represented in the IDS 30-item version) with respect to either their centrality (connectedness of each symptom with all other symptoms) or their relation to psychosocial functioning or life stress[8].

Furthermore, the criteria/signs/symptoms we use for diagnosis and assessment do not reflect the patient's concerns. Who is the judge? It has been documented that physicians differ significantly from patients in what they consider important for "being cured for depression". For physicians, the top five items are negative feelings, feeling down, little interest or pleasure, disrupted social life, and feeling tired, while for patients the top five items are "to what extent is life meaningful", "how much do you enjoy life", "how satisfied you are with

yourself", "how able you are to concentrate", and "negative feelings"[9]. Patients do attach more importance to restoration of positive mood and cognitive functioning than to decrease of negative mood. However, standard rating scales do not assess positive mood.

We feel that, before we can move from artisanal prescription patterns into precision medicine, patients' characteristics, beliefs and attitudes should be better taken into account, and diagnostic and assessment tools should be revised.

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Right patient, right treatment, right time: biosignatures and precision medicine in depression

In contrast to diagnostic changes in the rest of medicine, mental disorders are still considered as behavioral, implying that an exclusive focus on symptoms would yield a precise diagnosis[1]. Thus, even though depression is characterized by biological heterogeneity and variable symptom presentation, diagnosis and treatment recommendations are traditionally given without reference to individual variability in genes, brain structure, function and/or psychological factors. Rather, clinical and health characteristics (e.g., age, weight, medical comorbidities, depression severity) serve as the sole method for treatment selection, despite limited consistency of these characteristics to yield strong associations to treatment response. As a result, treatment selection remains a trial and error process, and only one third of patients achieve remission with the first medication prescribed, with even lower rates of sustained remission in the longer term[2,3].

Much of the previous research in depression treatment has focused on predictor variables – that is, characteristics of individuals that are associated with treatment response (or non-response), independent of treatment. More recently, increased research has focused on moderator and mediator variables. Moderators are pre-treatment variables that predict differential response to different treatments; mediators are variables whose change during the course of treatment predicts eventual treatment outcomes. Clearly, our prior focus on predictor variables has yielded inconsistent and inadequate findings, and, even with the recent attention to moderator and mediator characteristics, we have yet to determine which patient will respond to which treatment. What is needed, instead, is a comprehensive panel of variables encompassing both clinical characteristics and biological factors that can lead us to identify the right treatment for the right patient.

A comprehensive approach for targeted drug treatment and prevention is precision medicine, which takes into account the complex interplay between individual variability in clinical phenotypes, genes and brain function[4]. Treatments for cancer and chronic heart disease have developed these models and, as a result, we have reduced morbidity and mortality through the development of targeted therapies for these diseases. Yet, mental illness often lags far behind. Recent focus of the US National Institute of Mental Health on the Research Domain Criteria (RDoC) and research in genetics, proteomics and brain imaging suggest that biological measures (or biomarkers) may help us to understand the heterogeneity within the symptoms of depression and other mental illnesses[5]. Identification of biomarkers of preclinical depression or of response to drug treatment will be crucial in the development of precision medicine, being propelled by recent technological advances in large-scale biologic databases (such as the human genome and connectome projects), powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays), methods for detecting patterns of brain activity and structure, and effective computational tools for analyzing extremely large datasets.

Biomarkers are measurable characteristics of an organism that correspond to a particular physiological state. Biomarkers include compounds isolated from the blood, urine or other fluids as well as clinical, behavioral and neurocognitive parameters that are used to indicate the presence or severity of a particular disease state. Moderator biomarkers specify for whom or under what conditions the treatment works, and consequently help to clarify the best choice of inclusion and exclusion criteria or the best choice of patient stratification. Mediator biomarkers identify possible mechanisms through which a treatment might achieve its effect, and changes along with response to a particular intervention. Information gained from diagnostic or progression biomarkers should aid to tailor treatments for effective personalized medicine.

The development of biomarker predictors of antidepressant response languished after multiple candidates, most notably the dexamethasone suppression