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The role of depression pharmacogenetic decision support tools in shared decision making

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Abstract Patients discontinue antidepressant medications due to lack of knowledge, unrealistic expectations, and/or unacceptable side effects. Shared decision making (SDM) invites patients to play an active role in their treatment and may indirectly improve outcomes through enhanced engagement in care, adherence to treatment, and positive expectancy of medication outcomes. We believe decisional aids, such as pharmacogenetic decision support tools (PDSTs), facilitate SDM in the clinical setting. PDSTs may likewise predict drug tolerance and efficacy, and therefore adherence and effectiveness on an individual-patient level. There are several important ethical considerations to be navigated when integrating PDSTs into clinical practice. The field requires greater empirical research to demonstrate clinical utility, and the mechanisms thereof, as well as exploration of the ethical use of these technologies.

Keywords Pharmacogenetics · Antidepressants · Shared decision making · Decision support tool · Psychoeducation · Adherence · Therapeutic alliance

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Antidepressant effectiveness in the real world

Antidepressant medications are the mainstay of treatment for moderate to severe depression, however, their efficacy (degree of beneficial effect under ideal conditions, i.e. 100% adherence) is low (30% remission), and their effectiveness (degree of beneficial effect under real-world conditions) is often lower given poor adherence (13–60%) and premature discontinuation (33–42%) (Thase et al. 2010; Akincigil et al. 2007; Sheehan et al. 2008; Demyttenaere et al. 2001; Rush et al. 2006).

Patients often stop taking antidepressants due to remission, partial-response or non-response, lack of knowledge and disengagement, unrealistic expectations, and/or unacceptable side effects (van Grieken et al. 2014). The mean time to antidepressant discontinuation in Australia is 3 months in primary care and 4 months in specialist care (Mcmanus et al. 2004a). Only 38% of people are still on antidepressant therapy after 6 months (Mcmanus et al. 2004b).

It has been argued that a greater focus on the patient may be the best clinical strategy to improve these outcomes (Mulsant et al. 2014). Shared decision making (SDM) is a promising practice strategy with the capacity to improve education, adherence and hence outcomes (LeBlanc et al. 2015).

Engaging patients in their care with shared decision making

Shared decision making is a patient-centred approach to care in which the clinician and patient (including family members or caregivers) share a balanced role in treatment based on evidence-based practices aligned with the patient's values, goals, experiences and preferences (Raue et al. 2010; Charles et al. 1999; Slade 2017). This occurs through an open discussion of advantages, disadvantages and uncertainties of various options (Raue et al. 2010; Charles et al. 1999; Slade 2017). SDM acknowledges the patient as a valued partner and contributor to the treatment team, and it is hypothesised that greater patient involvement may lead to increased involvement and better engagement with care, increased treatment adherence, and greater satisfaction with care and reduced stigma—all of which contribute to outcomes (Slade 2017).

The ethical argument for SDM lies in principle-based ethics. SDM is a method of respecting and boosting the patient's sense of autonomy and ability to self-determine by recognising their role as an expert-by-experience, thereby reducing the power imbalance in the therapeutic relationship between them and the clinician, an expert-by-training (Slade 2017). This is likely to lead to an enhanced sense of self-efficacy regarding the selected treatment and perhaps improved outcomes (Stacey et al. 2014; Sirey et al. 2013). Ultimately, patients want SDM; it is the preferred decision making style over clinician-led and patient-led models, as demonstrated in a recent review (Schattner et al. 2006).

Certainly, adoption and acceptance of SDM is dependent on cultural context and patient's preferred communication style, as informed by their cultural background and preconceived ideas of health care, and the patient–doctor relationship. The findings of recent reviews suggest that some practitioners avoid the discussion of psychiatric diagnoses with patients of ethnic minority backgrounds for fear of reinforcing stigma or highlighting potentially conflicting values, communication styles and expectations of the doctor–patient relationship, exhibiting racism and perceptual biases, and language barrier (Milton and Mullan 2014; Schouten and Meeuwesen 2006). Nevertheless, health systems are moving towards patient-centred care models as it is becoming increasingly accepted that patient engagement in their care is vital, independent of ethnicity (Hawley and Morris 2017; Hibbard 2017). Striking the balance between enhancing patient autonomy and meeting their cultural needs and personal expectations may represent the *art of psychiatry* and SDM may thus exist within a spectrum rather than as a binary concept.

Limitations of shared decision making

The main limitation of SDM is an evolving evidence base (Alguera-Lara et al. 2017). SDM is a difficult area to study as it involves a conversation over a period of time drawing upon interpersonal skills that are not easily standardised, quantified or qualified. There is a great variability in what is considered SDM, giving rise to a plethora of possible interventions and no firm threshold for 'adequate' SDM activity. Trials are often limited to evaluating the use of specific tools to inform one-off treatment decisions (Slade 2017). A Cochrane review of SDM in people with long-term conditions found small positive effects on emotional health, physical health and self-efficacy (Coulter et al. 2015). These effects were enhanced by multiple contact points over time, greater integration with routine care, support for both clinicians and patients, and planning for all stages of the care cycle.

It is worthwhile also considering that at times, SDM may not be possible from the commencement of treatment, such as in the setting of psychosis or where a patient lacks capacity (Slade 2017). Here, a major treatment goal is the establishment of a solid therapeutic alliance where over time one can move towards concordance (Berk et al. 2010). We believe than in all other settings SDM ought to be the default.

Shared decision making in antidepressant treatment

Given the challenges of antidepressant management, patient engagement by way of SDM may be beneficial in alleviating depressive symptoms, such as helplessness and hopelessness, enhancing autonomy, self-efficacy and empowerment (LeBlanc et al. 2015); however, consequent improvement in medication adherence and clinical outcomes remains to be demonstrated. This is particularly germane to a disorder-like depression, characterised by disempowerment and a poor sense of self-efficacy, whereby SDM may reduce a cycle of demoralisation and helplessness exacerbating distress (Tecuta et al. 2015). There is a suggestion that individuals who indicate a preference for which treatment they would want between antidepressants and psychotherapy are more likely to respond to the modality of their preference, this being true of both modalities (Dunlop et al. 2012). The implication of this is that it is essential to understand the person's view of their difficulties, and that treatment needs to be concordant with this worldview. For example, the Treatment Initiation and Participation (TIP) programme, a protocolised and pragmatic psychosocial intervention to understand and target psychological barriers to depression care, such as

beliefs about medications, has been shown to improve both adherence and depression outcomes with antidepressants in primary care (Sirey et al. 2010, 2017).

While there are potential benefits to the use of SDM in the management of depression, hesitance around putting the principles into practice remains. A study of 1168 patients with depression (PHQ-9 score ≥ 7) reported only modest levels of involvement in treatment decisions (50.7 composite score, standard deviation 32.8) derived from "yes" responses to six questions on SDM. SDM scores varied by age group with older patients (45 and 33 for patients aged 50–64, and > 64 years, respectively; $P < 0.0001$) and those who have been in treatment longer (45.5 if treated for > 6 weeks; $P < 0.001$) reporting much less involvement in their care (Solberg et al. 2014). Identified clinician barriers to SDM include a lack of time, skills, and resources and concerns that patients would make inappropriate choices (Stacey et al. 2017). However, it has been demonstrated that SDM does not prolong consultations and is applicable to patients of all ages, social and educational backgrounds, and levels of health literacy (LeBlanc et al. 2015; Durand et al. 2014). Naturally, specific techniques utilised must be flexible for different population groups. Studies and clinical guidelines exist for specific populations, including the elderly (Raue et al. 2010) and young (ORYGEN 2016).

Expectations and shared decision making in antidepressant treatment

The most prominent predictor of outcome in psychotherapy and psychopharmacology treatment is expectation, and this is a major contributor to the placebo effect (Rief and Glombiewski 2017). Individuals with depression tend to hold negative expectations of therapy (Rief and Glombiewski 2016) and SDM may modify these expectations and increase the likelihood of response to treatment. While it is unclear how much of the benefit of SDM is attributable to placebo, the effect may be a powerful mechanism in overcoming therapeutic inertia and encouraging patients to engage with services and undertake treatment.

We believe SDM is also a potential mechanism for mitigating the nocebo effect. The nocebo effect, from the Latin 'I will harm', or better known as the alter-ego to the placebo effect, describes de novo adverse reactions to treatment which are either not attributable to the physical or pharmacological properties of an agent, or are an amplified adverse response to an agent (Data-Franco and Berk 2013). Prior conditioning, i.e. attributing previously experienced side effects to an entire class of drugs, and/or negative expectations regarding treatment, is implicated in the nocebo effect, as is a disrupted attachment style, often linked to early childhood attachment difficulties or trauma. This results in an increased risk of a hostile-dependent relationship with clinical care, often manifested by distrust and anxiety regarding treatment and increased risk of the development of nocebo reactions. The nocebo effect is postulated to involve the down-regulation of cholecystokinin, dopamine and endorphin pathways (Dodd et al. 2015). The nocebo effect is an important confounder in clinical trials, where it is associated with higher treatment discontinuation rates, lower sample sizes and therefore higher false negative rates (Data-Franco and Berk 2013; Dodd et al. 2015). Clinically, it may lead to poorer treatment outcomes, perception of adverse reaction and premature treatment cessation. The nocebo effect in antidepressant therapy has been explored by examining the adverse reactions experienced by patients in placebo arms of randomised control trials. While it was common for placebo-treated participants to report adverse events, there were no emerging trends supporting either a conditioning or expectancy hypothesis, suggesting a greater complexity and multifactorial nature to the phenomenon (Dodd et al. 2015).

While it is not yet completely understood, the nocebo effect can be mitigated by recognising the phenomenon, identifying if the patient fits the 'at risk' profile and incorporating techniques to minimise the nocebo response. Patients who have had prior adverse treatment experiences, prior trauma or early attachment difficulties, anxiety, depression, type-A behaviour patterns, neurotic or pessimistic traits, are female or have pre-existing somatic symptoms are more likely to experience a nocebo response (Data-Franco and Berk 2013). The clinical management component is illuminatingly simple, and relies on the basic principles of informed consent, sharing information, shaping expectations and a positive and considerate physician attitude (Data-Franco and Berk 2013)—elements that ought to form the basis of any clinical encounter. Patients increasingly rely on the internet for healthcare information. It is interesting to posit that the phenomena of patients 'Googling' their medications could intensify negative expectancy and nocebo effect. Conversely, other emerging technologies may help to improve positive expectancy—tools, such as decisional aids and pharmacogenetic decision support tools (PDSTs) (Lemire et al. 2008).

Decisional aids promote shared decision making

Decisional aids promote SDM by highlighting key aspects of treatments, including antidepressant therapies in depression, to facilitate choosing a treatment that is more

Table 1 Summary of randomised controlled trials evaluating decision support tools in major depressive disorder (MDD)

Author/s	Study design	Intervention	Sample population	Primary outcomes	Key limitations
Perez et al. (2017)	Cluster randomised controlled trial in 13 primary care centres	Web Platform (http://PyDeSalud.com) to promote and facilitate citizens' empowerment and engagement in the decisions concerning their health	Adults (18 + years) with DSM-IV MDD in primary are decision aid ($n = 68$) or usual care ($n = 79$)	Intervention significantly improved knowledge ($P < 0.001$) and decisional conflict ($P < 0.001$), and no differences were observed in treatment intention, preferences for participation, or concordance	Absence of baseline assessment Limitations to blinding patients
LeBlanc et al. (2015)	Cluster randomised controlled trial in ten primary care practices	DMC, a series of cards, each highlighting the effect of the available antidepressant options on an issue of importance to patients for use during face-to-face consultations	Adults (18 + years) with depression (PHQ9 $\geq$ 10)	DMC significantly improved patients' decisional comfort, knowledge, satisfaction, and involvement. It also improved clinicians' decisional comfort and satisfaction. There were no differences in encounter duration, medication adherence, or improvement of depression control between arms	Lack of blinding Significant loss to follow-up
Loh et al. (2007)	Cluster randomised controlled trial in primary care centres	Physician programme to enhance skills for engaging patients in care. Decision aids used for education re diagnosis, treatment options, assessing health beliefs, coping strategies, family engagement	405 adult patients with depression via primary care doctor judgement. 135 in intervention group, 76 in control group	Physician facilitation of patient participation improved significantly and to a greater extent in the intervention compared to the control group. There was no intervention effect for depression severity reduction. Doctor facilitation of patient participation, patient-rated involvement, and physician assessment of adherence improved only in the intervention group. Patient satisfaction at post-intervention was higher in the intervention group compared to the control group. The consultation time did not differ between groups	Physicians not patient assigned to cluster randomisation Significant patient characteristic difference between groups

DMC Depression Medication Choice, *PHQ* Patient Health Questionnaire

appropriate for the patient; for example, one that is least likely to cause intolerable side effects or safety concerns. Decision support tools are particularly useful in the primary care setting, where depressive symptoms are present in nearly 70% of patients (Robinson et al. 2005). In the way of theoretical side-effect profiles, there exists a repository of decisional aids online that allows clinicians and patients compare the available medications (IPDAS 2013). The Depression Medication Choice (DMC) encounter decision aid has been developed by the Mayo Clinic. The decision aid, formatted as laminated $4'' \times 10''$ cards, presents general considerations about antidepressant efficacy and then side effects in terms that matter to patients: weight change, sleep, libido, discontinuation, and cost. The tool is available free online for clinical use (Mayo 2011). A study of 117 clinicians and 301 patients with PHQ-9 scores of 10 or higher assessed the use of DMC compared to usual care (UC), showed that the use of the DMC aid significantly improved patients' decisional comfort (DMC, 80 vs. UC, 75%; $P = 0.02$), knowledge (DMC, 65 vs. UC, 56%; $P = 0.03$), satisfaction [risk ratio (RR), from 1.25 ($P = 0.81$) to RR, 2.4 ($P = 0.002$) depending on satisfaction domain], and involvement (DMC, 47 vs. UC, 33%; $P < 0.001$) while also improving clinician decisional comfort (DMC, 80 vs. UC, 68%; $P < 0.001$) and satisfaction (RR 1.64, $P = 0.02$) (LeBlanc et al. 2015). However, there was no difference in medication adherence and improvement in depression rating between the two arms at the end of the 6-month follow-up period. See Table 1 for RCTs evaluating decision support tools in MDD. An

additional decisional aid involves the use of pharmacogenetic testing to individualise pharmacological therapy on the basis of genetic variations, which may determine drug tolerability, efficacy and effectiveness.

Pharmacogenetic decision support tools as decisional aids in shared decision making

Pharmacogenetic decision support tools (PDST) in depression are increasingly topical in clinical care as a potential strategy to improve treatment outcomes (Rosenblat et al. 2017). There are numerous PDSTs available. At a minimum, the tools sequence CYP2D6 and CYP2C19 variants of the CYP450 liver enzyme system, a key pharmacokinetic determinant (Bousman and Hopwood 2016). Some tools also sequence one or more central nervous system-based determinants, such as serotonin receptors or transporters, dopamine receptors and blood–brain barrier transporters (Peterson et al. 2016). There are varying levels of evidence for the genes included in commercial PDSTs. The levels of evidence are outlined in Fig. 1 and are based on the PharmGKB knowledge base and clinical annotation. Many tools lack the evidence of clinical utility (i.e. trials comparing the intervention against treatment as usual) and existing trials are summarised in Table 2 (Rosenblat et al. 2017; Pérez et al. 2017). The few published randomised control trials have mixed findings (Singh 2015; Winner et al. 2013). To date, no randomised controlled trials have been independently replicated to moderate for bias, nor have any tools been compared head-to-head.

Whilst much optimism surrounds the use of PDSTs in depression, published systematic reviews have been cautious in recommending their adoption into practice prior to further validation (Rosenblat et al. 2017; Bousman and Hopwood 2016; Peterson et al. 2017). Nevertheless, survey data shows over 80% of doctors believe that psychiatric PDSTs will become a standard of care (Walden et al. 2015; Thompson et al. 2015). These tools may represent an important facet of SDM by moving toward a more scientifically driven prescribing strategy, and enriching two-way conversations between doctors and patients involving an exchange of values and knowledge, and enhancing engagement and the treatment alliance.

Empirical considerations of pharmacogenetic decision support tools

The role of placebo and nocebo in PDSTs ought to also be explored empirically to determine what role they have in

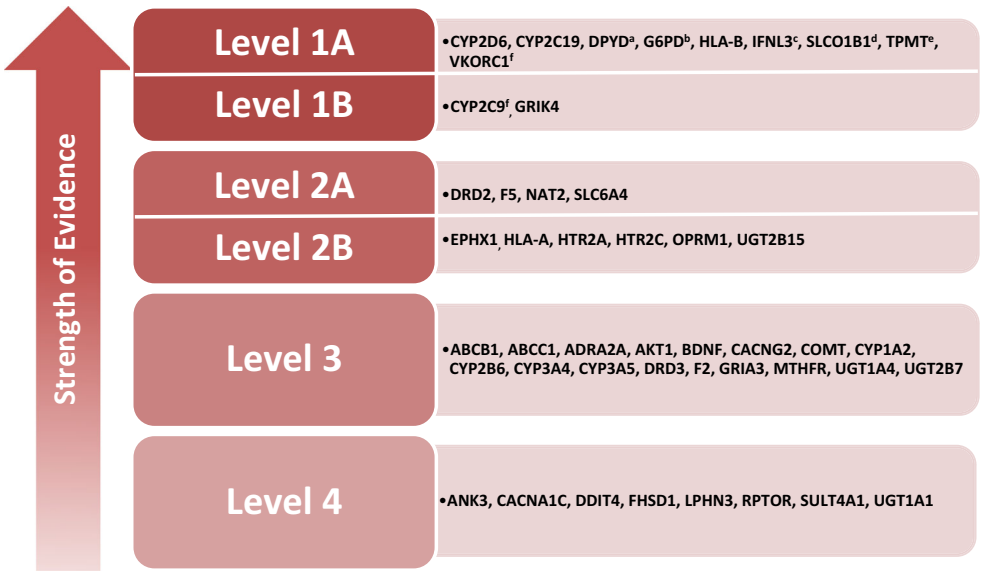

Fig. 1 Level of evidence for each of the genes included in commercial pharmacogenetic tools in psychiatry (adapted from Bousman and Hopwood 2016). Level of evidence is based on the PharmGKB knowledge base and clinical annotation. Level 1A: a variant(s) in these genes has been endorsed by the Clinical Pharmacogenetics Implementation Consortium or medical society or has been implemented in a major health system. Level 1B: a variant(s) in these genes shows an association with strong effect size and has been replicated in more than one cohort. Level 2A: a variant(s) has been located within a "very important pharmacogene" with a small-to-moderate effect size and evidence for replication is scarce. Level 2B: a variant(s) has been located in a gene that is not a "very important pharmacogene" with a small-to-moderate effect size and evidence for replication is scarce. Level 3: a variant(s) in these genes shows an association but has yet to be replicated or has been evaluated in multiple studies but lacks clear evidence of association. Level 4: a variant(s) in these genes has little or no evidence for association or is based on preclinical studies. Gene interacts with *fluoropyrimidines (chemotherapeutic), [†]rasburicase, [‡]PEG-interferon-α-containing regimens, [§]simvastatin, [¶]immunosuppressive agents (e.g., azathioprine), and |warfarin

Table 2 Summary of Clinical trials evaluating the clinical utility of pharmacogenetic decision support tools in major depressive disorder (MDD)

Author/s	Study design	Target genes	Sample population	Primary outcomes	Key limitations
Hall-Flavin et al. (2012)	8-week non-randomised open-label prospective cohort study	CYP2D6, CYP2C19, CYP1A2, SLC6A4, HTR2A	Adults (18–75 years) with DSM-IV MDD diagnosis (HDRS score > 14) allocated into guided arm ($n = 22$) and non-guided arm ($n = 22$)	30.8% reduction in HDRS score in the guided arm (s 18.2% reduction in non-guided arm ($P = 0.04$)	Non randomised allocation Open-label study Partial industry funding Recruitment bias
Hall-Flavin et al. (2013)	8-week non-randomised open-label prospective cohort study	CYP2D6, CYP2C19, CYP1A2, SLC6A4, HTR2A	Adults (18–72 years) with DSM-IV MDD diagnosis (HDRS score > 14) allocated into guided arm ($n = 114$) and non-guided arm ($n = 113$)	46.9% reduction in HDRS score in the guided arm vs. 29.9% reduction in non-guided arm ($z = 3.14$, $P < 0.0001$) 26.4% remission rate in the guided arm vs. 12.9% in the unguided arm (OR = 2.42; 95% CI 1.09–5.39; $P = 0.03$)	Non randomised allocation Open-label study Partial industry funding Recruitment bias
Winner et al. (2013)	10-week randomised double-blind prospective RCT	CYP2D6, CYP2C19, CYP1A2, SLC6A4, HTR2A	Adults with DSM-IV MDD diagnosis (HDRS score > 14) randomised into guided arm ($n = 26$) and non-guided arm ($n = 25$)	30.8% reduction in HDRS score in the guided arm vs. 20.7% reduction in non-guided arm ($P = 0.28$) Response and remission favoured the guided group however this did not reach statistical significance	Partial blinding (patient only) Full industry funding Findings are not clinically significant Recruitment bias
Brennan et al. (2015)	3-month naturalistic unblended prospective study	CYP2D6, CYP2C19, CYP3A4, SLC6A4, 5HT2C, DRD2, CACNA1C, ANK3, COMT, MTHFR	Adults (> 18 years) with an active psychiatric diagnosis ($n = 685$) 70% of sample had primary diagnosis of mood disorder including 42.6% with MDD	Mean QIDS-SR score decreased to 8.9 at 1 month and 7.8 at 3 months ($P < 0.001$) Among patients with primary mood disorder, QIDS-SR decreased to 9.6 at 1 month and 7.9 at 3 months ($P < 0.001$) 38% of patients achieved remission (score < 5) and 39% showed response (> 50% reduction in score), indicating clinical efficacy for 77% of patients with a mood disorder	No control group No blinding Non-uniform sample Full industry funding Recruitment bias
Singh (2015)	12-week prospective double-blind RCT	ABCB1, ABCC1, CYP2C19, CYP2D6 and UGT1A1	Caucasian adults (> 18 years) with DSM-V MDD diagnosis (HDRS score > 18) randomised into a guided arm ($n = 74$) and non-guided arm ($n = 74$)	72% remission rate in the guided arm vs. 28% remission rate in the non-guided arm (OR = 2.52, 95% CI 1.71–3.73, $P < 0.0001$) with NNG = 3 (95% CI 1.7–3.5) to produce an additional remission	Partial blinding (patient only) Fully industry funded Recruitment bias Report guided dosing only (not drug choice)
Perez et al. (2017)	12-week prospective double-blind RCT	ABCB1, AKT1, BDNF, CACNG2, CES1, COMT, CRHR1, CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, DDIT4, DRD3, EPHX1, FCHSD1, GRIK2, GRIK4, HLA-A, HTR1A, HTR2A, HTR2C, LPHN3, NEFM, OPRM1, RGS4, RPTOR, SLC6A4, UGT2B15	Predominantly Caucasian adults (> 18 years) with DSM-V MDD diagnosis (CGI-S ≥ 4) randomised into a guided arm ($n = 155$) and non-guided arm ($n = 161$)	47.8% responders in the guided arm vs. 36.1% in the non-guided arm (OR = 1.62, 95% CI 1.00–2.61; $P = 0.0476$) Greater reduction in HDRS in the guided group at 6 weeks ($P = 0.0364$) but not at 12 weeks ($P = 0.0771$) Among patients who had previously failed 1–3 treatments ($n = 173$), significantly reduced PGI-I score at 12 weeks, and HDRS score at both 6 and 12 weeks	Partial blinding (patient only) Fully industry funded Recruitment bias

CGI-I Clinical Global Impressions—Improvement, *CGI-S* Clinical Global Impressions—Severity of Illness, *HDRS* 17-item Hamilton Depression Rating Scale, *NNG* number needed to genotype, *QIDS-SR* 16-item Quick Inventory of Depression Symptomatology Scales—Subject Rated

clinical utility. The traditional 'gold standard' of double-blinding in these trials may have limited use in pharmacogenetics, i.e. blinding raters and patients. Patient blinding mitigates the SDM process and hence it likely reduces the clinical utility of the PDST. Therefore, single-blinding of just the rater, and not the patient, may be advisable. Constructing studies comparing single-blind and double-blind methodologies will parse out the mechanisms of these tools.

Ethical considerations of pharmacogenetic decision support tools

Pharmacogenetic decision support tools use may also signal a shift in the doctor–patient relationship in ethical terms. Unlike other areas of medicine where diagnoses can be substantiated by objective investigation findings, medical imaging being a clear example, this is not the case in psychiatry. Often this leaves the patients seeking for 'proof' of their diagnosis and recommended treatment. It has been suggested that PDSTs, as a somewhat biological measurement, may contribute objective weight to the proposed treatment and could be misused to coerce patients into pharmacologic management, thereby undermining SDM. Reciprocally, where the patient initiates and/or finances the test, the physician may feel pressured to apply the results thereby undermining their own clinical judgement and experience. This is a misuse of PDSTs as they are neither objective nor prescriptive and their entire premise is to support physician's choice of medication while minimising harm to the patient. This too, raises ethical questions, whereby in the setting of an evolving evidence-base, it is uncertain when a PDST ought to be initiated and whether a delay in its use could be unethical given that there is potential for unguided and thus harmful therapy. It ultimately is important for clinicians to respect their patient's wishes, to be aware of the evidence base, for the academic sector to scrutinise the field, and for clinical practice guidelines to provide suggestions on use.

Conclusion

Shared decision making involves the engagement of patients and their supports in making decisions on investigations and treatments. Patient investment and empowerment in their care may improve adherence to antidepressant medications and treatment effectiveness. Decision aids, such as PDSTs, are a relevant part of this concept, and appear useful in enhancing patient knowledge of their medication metabolism, medication efficacy and side effects. The combination of greater patient involvement, the use of decision aids and PDSTs to inform the discussion could markedly increase the real-world effectiveness of antidepressants. Further empirical research is required on this topic.

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