

PGx for Mental Health and Pain medications

ANTIDEPRESSANTS

THE STAR*D STUDY

Finding the right antidepressant can take too long for many individuals. The STAR*D study showed that evaluation of antidepressant efficacy in the treatment of major depressive disorder usually takes more than 4 weeks and 60% patients do not show significant remission after 12 weeks of treatment even with a sufficient dose of antidepressant¹.

In 2008, Kemp and co-authors commented: 'Since depression is associated with substantial morbidity and family burden, it is unfortunate and demanding on health resources that patients must remain on their prescribed medications for at least 4 weeks without knowing whether the particular antidepressant will be effective. Studies have suggested a number of predictors of treatment response.... including genetic markers².'

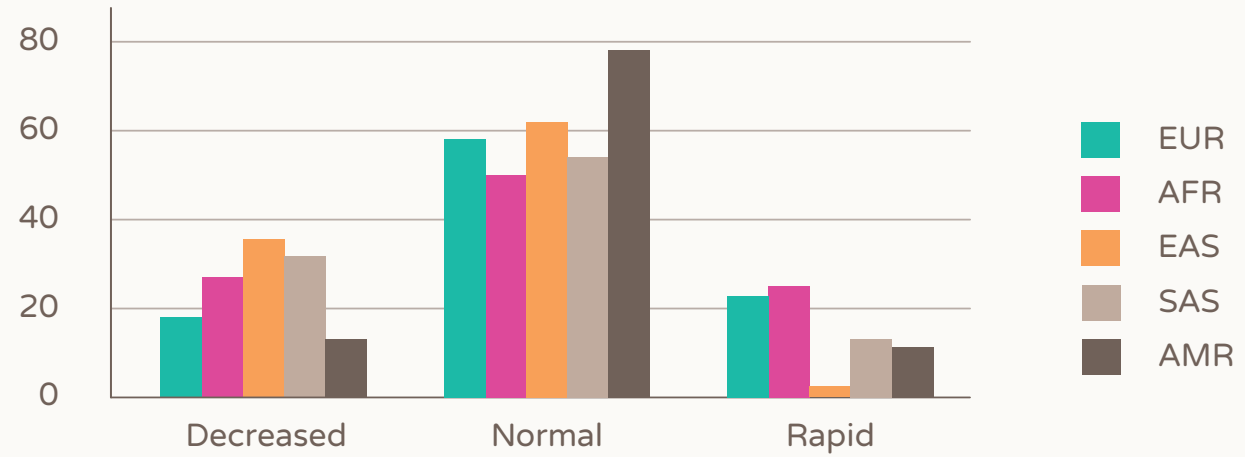
Common **CYP450** enzymes that metabolize antidepressant, antianxiety and antipsychotic medications

Tricyclic anti-depressants were among the earliest antidepressants developed but there has been a decline in their use due to the occurrence of undesirable side effects. Functional consequences of variations in **CYP2D6** and **CYP2C19** genes affect activity of the enzymes (Figure 1) and the efficacy and safety of tricyclic antidepressants, with some drugs being affected by **CYP2D6** and others by both enzymes.

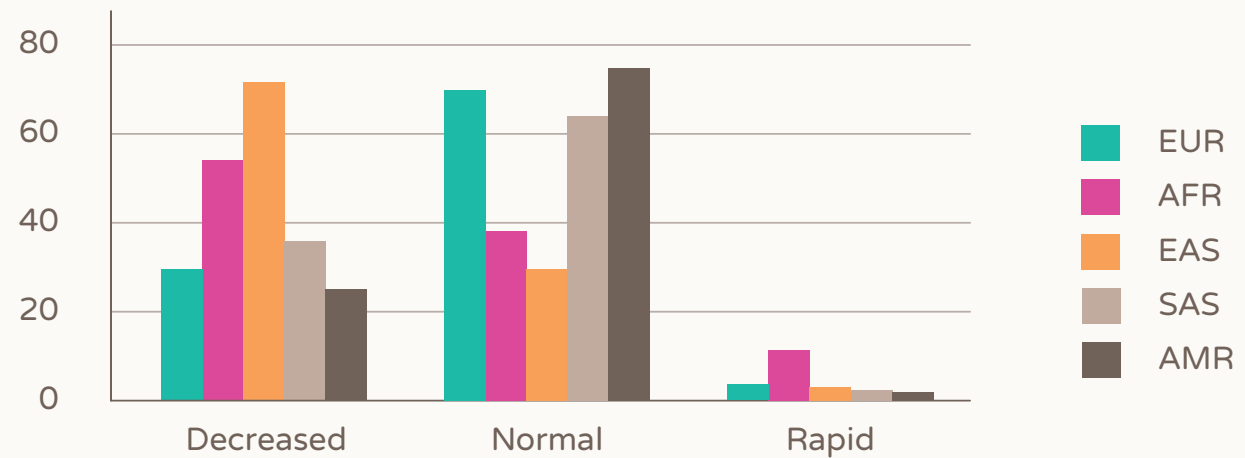
1. Warden D et al. The STAR*D Project results: a comprehensive review of findings. *Curr Psychiatry Rep.* 2007;9:449-459.

2. Kemp AH et al. Improving the prediction of treatment response in depression: integration of clinical, cognitive, psychophysiological, neuroimaging, and genetic measures. *CNS Spectr.* 2008;13(12):1066-1086

Frequency of *CYP2C19* Activity



Frequency of *CYP2D6* Activity



EUR: Europeans, AFR: Africans, EAS: East Asians, SAS: South Asians, AMR: Admixed Americans
Figure1: Variability in *CYP2C19* and *CYP2D6* activity in major populations
Adapted from: Y Zhou et al., *Clin Pharmacol Ther* (2017) 102:688-700

Variability in **CYP2D6** and **CYP2C19** activity also influence metabolism of Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin-norepinephrine reuptake inhibitors (SNRI) while bupropion is metabolized into its active compound almost exclusively by **CYP2B6**. Common **CYP450** enzymes also metabolize antianxiety drugs like diazepam and anti-psychotics like clozapine and haloperidol.

PGx of ADHD medications

Reviews on the role of genetic variants mediating responses to attention/deficit hyperactivity disorder (ADHD) medication generally indicate inconclusive results. However, metabolism of atomoxetine by **CYP2D6** is well established and recommendations are available. Variations in the **OPRM1** gene have been shown to modulate amphetamine-induced euphoria.

Impact of **CYP2D6** Poor Metabolizer on hospitalization for major depressive disorder

Variations in the **CYP2D6** gene significantly impacted utilization of psychiatric hospitalization services, specifically leading to longer Length of Stay for patients with major depressive disorder, the leading cause of disability in North America. **CYP2D6** Poor Metabolizers had significantly longer mean stay than Normal or Rapid Metabolizer³. As the cost of genotyping decreases and the number of patients being treated for psychiatric conditions increases, the authors advocate the use of PGx testing as a clinical tool to improve quality of care and cost savings.

Economic impact of PGx-guided therapy

To assess the economic impact of PGx-based treatment on healthcare resource utilization, a study⁴ evaluated the ability of a PGx test to impact direct and indirect healthcare costs and medical utilization for patients with depression and anxiety. The authors captured disability claims, missed work and multi-specialty healthcare appointments. PGx-guided psychiatric medication selection resulted in better medical outcomes and productivity cost savings.

3. Ruaño G et al. Length of psychiatric hospitalization is correlated with **CYP2D6** functional status in inpatients with major depressive disorder. *Biomark Med.* 2013;7(3):429-39

4. Winner J et al. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. *Transl Psychiatry.* 2013;3:e242

Randomized Controlled Trials in hospital setting

A 12-week, double-blind, parallel, multi-center randomized controlled trial in patients with major depressive disorder was conducted in 18 hospitals to evaluate effectiveness of PGx-guided testing therapy⁵. Patients requiring antidepressant medication de novo or changing medication were randomized to PGx-guided treatment or treatment as usual. The study included patients who had failed multiple previous treatments and 65% of the population in this study were regarded as refractory.

Among subjects having received 1 to 3 previous psychiatric treatments, statistically significant differences were identified at 12 weeks in the percentage of patients with a positive response to treatment. 52% of patients on PGx-guided therapy had a positive response to treatment compared to 31% in the control (p-value = 0.01).

Randomized Controlled Trials in primary clinics

As a majority of patients with anxiety and depression are treated at primary care clinics, a prospective, randomized double-blind trial enrolled patients from 20 independent clinical sites. Besides Psychiatry, the clinics specialized in Internal medicine, Family medicine, Gynaecology and the study population included patients with broad range of severities for depression and anxiety or comorbid patients displaying both⁶.

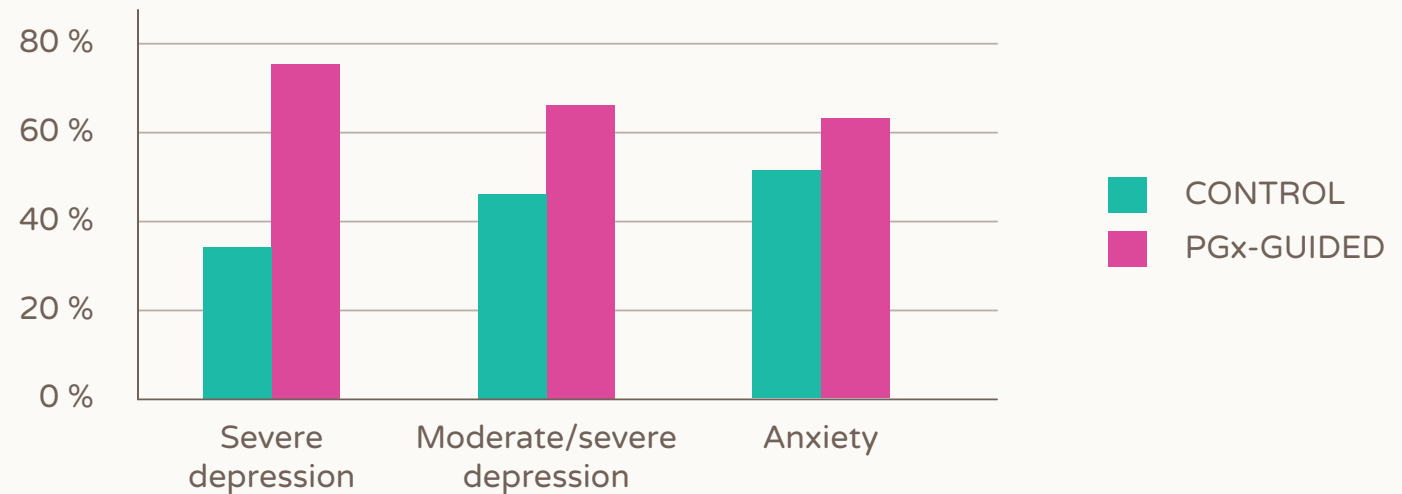
Statistically significant improvements for PGx-guided therapy compared to controls were observed in all groups (Figure2). In patients with depression, response rates (p-value = 0.001) and remission rates (p-value = 0.02) were significantly higher in the PGx-guided group compared to controls at 12 weeks.

For patients with moderate or severe depression, PGx-guided treatment improved remission rates 35% vs. 13% compared to control (p-value=0.02) at 12 weeks.

PGx-guided therapy for patients with anxiety improved HAM-A scores at 12 weeks (p-value = 0.02), along with higher response rates (p-value = 0.04).

5. Pérez V et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. *BMC Psychiatry*. 2017;17(1):250
6. P. Bradley et al. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: A randomized clinical trial demonstrating clinical utility. *J Psychiatr Res*. 2018;96:100-107

Response rates for patients with depression and anxiety



PGx in child and adolescent psychiatry

Depressive, anxiety disorders and ADHD are common in children and adolescents and multiple medications are available. Due to toxicity-related side effects (observed in 20–70% of patients) medications are often initiated at low doses to minimize side effects. This can increase the risk of under-treatment, especially in Ultrarapid Metabolizers, leading to medication change due to lack of treatment response⁷. Though PGx-guided dosing is common in paediatric oncology, paediatricians have limited PGx data to guide choice of ADHD, depression and anxiety medications⁸. While more research is needed, PGx has the potential to decrease morbidity and side effects while improving treatment response.

PGx recommendations and guidelines

Recommendations from PharmGKB, CPIC and DPWG on gene-drug interactions for **TCA**, **SSRI**, **SNRI**, antipsychotic and anti-anxiety medications are used for generating Pillcheck Reports. Combinatorial guidelines for **TCA**, using **CYP2D6** and **CYP2C19** genotyping, used in Pillcheck Reports are recommended by CPIC.

Figure 2: Response rates for patients with depression and anxiety
Adapted from: P. Bradley et al. 2018 J Psychiatr Res 96:100-107

7. Wehry AM et al Pharmacogenomic Testing in Child and Adolescent Psychiatry: An Evidence-Based Review. *Curr Probl Pediatr Adolesc Health Care*. 2018;48(2):40-49

8. Tulisak AK et al. Antidepressant Prescribing by Pediatricians: A Mixed-Methods Analysis. *Curr Probl Pediatr Adolesc Health Care*. 2017;47(1):15-24

PAIN MEDICATIONS

Some individuals do not get pain relief from standard doses of commonly prescribed pain medication while others suffer from an overdose on being prescribed the same. The analgesic efficacy of opioids is found to vary greatly, while **NSAIDs**, can result in adverse side effects for some patients.

OPIOID METABOLISM AND VARIATIONS IN *CYP2D6*

Codeine, the most commonly prescribed opioid analgesic, is a pro-drug metabolized by ***CYP2D6*** to morphine for pain relief. In Ultrarapid Metabolizers, duplications in the ***CYP2D6*** gene result in increased enzyme activity and increased morphine production that can lead to respiratory depression on a standard dose of codeine. Poor *CYP2D6* Metabolizers get negligible pain relief from a standard dose of codeine as variations in the gene result in decreased function of the enzyme, producing little or no morphine. Similarly, oxycodone, hydrocodone and tramadol are metabolized by ***CYP2D6*** to the active metabolite, oxymorphone, hydromorphone and O-desmethyltramadol, respectively.

Pain management for Poor ***CYP2D6*** metabolizers can be complicated. Post-operative patients with little or no ***CYP2D6*** activity, endure pain until medications are switched⁹. In a post-operative setting, knowledge of patient's *CYP2D6* metabolic status can help with the selection of appropriate pain medications.

OPIOID RESPONSE AND VARIATIONS IN *OPRM1*

Morphine and fentanyl exert their analgesic effect primarily via the μ -opioid receptor encoded by the ***OPRM1*** gene. Variations in the ***OPRM1*** gene influence pain management of postoperative patients, providing valuable information on individual analgesic doses requirements to achieve satisfactory pain control¹⁰.

9. Foster A et al. Complicated pain management in a ***CYP450 2D6*** poor metabolizer. *Pain Pract.* 2007;7(4):352-356

10. Hwang IC et al. ***OPRM1 A118G*** gene variant and postoperative opioid requirement: a systematic review and meta-analysis. *Anesthesiology* 2014;121(4):825-834

METHADONE AND VARIATIONS IN CYP2B6

Methadone, a synthetic opioid with morphine-like effects is commonly used for treatment of opioid addiction, but also in the treatment of chronic pain. It is metabolized by **CYP2B6** and **CYP3A4**. Specific variations in the **CYP2B6** gene result in decreased clearance of methadone.

NSAID AND VARIATIONS IN CYP2C9

Celecoxib, a COX-2 selective inhibitor, is mainly metabolized by **CYP2C9** and Poor **CYP2C9** Metabolizers have significantly reduced clearance of celecoxib. A multicenter, case–control study to assess whether Intermediate and Poor **CYP2C9** metabolizers have an increased risk for NSAID-related upper gastrointestinal events concluded that Poor Metabolizers have a significantly increased risk for upper gastrointestinal bleeding¹¹.

Flurbiprofen, a COX non-selective inhibitor, is metabolized to 4-hydroxiflurbiprofen by **CYP2C9**, and Poor **CYP2C9** Metabolizers have significant reduction in flurbiprofen metabolism with a simultaneous decrease in clearance.

TCA, SSRI, SNRI AND ANTICONVULSANTS FOR CHRONIC PAIN

TCA's like doxepine, **SSRIs** and **SNRIs** are used as adjuvant therapy in the treatment of chronic pain. Anticonvulsants like carbamazepin are also effective for neuropathic pain. However, use of carbamazepin should be avoided in **HLA-B* 1502** carriers to prevent Stevens–Johnson syndrome and toxic epidermal necrolysis.

Absence of PGx markers for gabapentin

Newer anticonvulsants, such as gabapentin, have shown promise in chronic pain management. The **CYP450** enzymes do not metabolize gabapentin.

11. Figueiras A et al. **CYP2C9** variants as a risk modifier of **NSAID**-related gastrointestinal bleeding: a case-control study. *Pharmacogenet Genomics*. 2016;26(2):66-73

Cannabinoids in pain management

CYP2C9 and **CYP3A4** enzymes mediate clearance of cannabinoids and **Nabilone** and **Marinol**, synthetic compounds that mimic delta-9-tetrahydrocannabinol (THC). The drug label for **Nabilone** warns that exposure is 3 times higher in poor **CYP2C9** metabolizers as compared to Normal Metabolizers. It is expected that poor **CYP2C9** metabolizers will have an enhanced clinical response, particularly when treated with **CYP3A4** inhibitors.

When is **cannabinoid** use warranted?

Poor **CYP2D6** Metabolizers will not get pain relief with pro-opioids such as oxycodone and not metabolize many **SSRIs**, **TCAs**, **SNRIs**. They will need morphine or fentanyl and cannabinoids can also be considered for their pain management. Similarly, for Ultrarapid **CYP2D6** metabolizers most **SSRIs**, **TCAs** and **SNRIs** will be ineffective and pro-opioids increase their risk of accidental overdose and addiction. Therefore, morphine or fentanyl may be needed and cannabinoids can be considered. Patients with two **OPRM1** variations and poor response to opioids may need **NSAIDs** or cannabinoids for pain management.

Benefits of PGx-guided analgesics in abdominal surgery

The impact of PGx-guided selection of analgesics following major abdominal surgery within an Enhanced Recovery Program (ERP) of a hospital was studied in a series of open and laparoscopic surgery. PGx-guidance resulted in frequent modifications of the analgesic program, resulting in excellent analgesia with a 50% reduction in narcotic consumption, and a reduced incidence of analgesic related side effects compared to the standard **ERP**¹².

PGx-guided, patient-centric analgesics can improve standard ERP's in hospitals resulting in a reduced narcotic regimen providing early and durable pain control with fewer narcotic related side effects.

IN CONCLUSION

Inclusion of PGx in medication management can enhance prescribing decisions and is becoming the standard of care for drugs with PGx guidelines.

For more information on Pillcheck, a PGx test optimized for the multi-ethnic Canadian population, please refer to www.pillcheck.ca website.