ISSN: 2572-4037

Serani et al. Int J Psychol Psychoanal 2019, 5:041
DOI: 10.23937/2572-4037.1510041
Volume 5 | Issue 1
Open Access

International Journal of
Psychology and Psychoanalysis

REVIEW ARTICLE

# Personalized Medicine and Psychoanalysis: How Pharmacogenomic Testing Facilitates Depression Treatment

***Deborah Serani****

*Derner Institute of Advanced Psychological Studies, Adelphi University, USA*

***Corresponding author:** *Deborah Serani, Psy.D., Derner Institute of Advanced Psychological Studies, Adelphi University, 12 Ivy Hill Drive, Smithtown, New York, 11787, USA, Tel: 631-366-4674*

**Abstract**

Pharmacogenomic testing offers enormous potential to manage mental disorders like depression. But many psychoanalysts aren't aware of its value and biotechnical power. This article explains how this form of personalized medicine can be used to aid in the treatment of patients with depression. With over 20 medications approved by the FDA to treat depression, and many others recommended for off-label use, treatment failure with antidepressants commonly occurs in clinical practice. Inviting genetic testing into the treatment plan when working with depressed patients can reduce the rate of medication failure, improve antidepressant compliance and more accurately address resistance in analysis.

**Keywords**

Antidepressants, Cytochrome p450, Depression, Genetic testing, Medication, Personalized medicine, Pharmacogenomics, Psychoanalysis, Treatment resistant depression

## Introduction

In 2003, the human genome was sequenced successfully, bringing with it new discoveries, insights and scientific technologies. The *Human Genome Project* was a feat unto itself, cracking open the door toward a deeper understanding of genes and environment [1]. When reading about it, I wondered, "*How could this science help mental illness*?" I thought further, suspecting it'd be decades before mental illness and genetics would get time under the microscope.

In truth, it took less than a decade for genetics to root itself in a very important niche in mental health. The specific science, called *pharmacogenomics*, is defined as the identification of how one's genes metabolize and process antidepressant, psychotropic and other medications in the body [2,3].

## Personalized Medicine

The traditional way of prescribing medicine has always been based on the likelihood that each drug will work equally well in the entire population. Dose adjustments are based on physical variations, such as height and weight, with most drug manufacturers offering a "one size fits all" approach. The new way of prescribing medicine - once considered science fiction - is having tailor made medicines for each person. And it's available now. Pharmacogenomic testing is more casually known as *personalized medicine* or *precision medicine* and refers to the use of genetic testing to improve the safety, effectiveness, and health outcomes of patients taking medication [4,5].

Pharmacogenomic testing offers enormous potential to manage diseases and illnesses like depression. But many therapists aren't aware of its value and biotechnical power. Some clinicians have never heard of the term *Cytochrome p450* or that a genetic test can determine target-specific medications for patients. Others might be familiar with genetic testing, but mistakenly believe it's pricey. Or don't know it's fully covered by Medicare and insurance companies. Others practitioners aren't aware of the various genetic panels offered, what they do and how to interpret the results [6]. Additionally, studies suggest the general public has varying genetic literacy about the usefulness of tests, and as such, don't utilize this biotechnology to advance their health [6].

**Citation:** Serani D (2019) Personalized Medicine and Psychoanalysis: How Pharmacogenomic Testing Facilitates Depression Treatment. Int J Psychol Psychoanal 5:041. doi.org/10.23937/2572-4037.1510041

**Accepted:** June 12, 2019: **Published:** June 14, 2019

Regardless of the reasons why pharmacogenomics is still not well known, *Cytochrome p450* testing needs more clinical application. Its utility is enormously far-reaching for our patients and for our work as psychoanalysts.

## Psychoanalysis and Medication

Sigmund Freud, a neurologist by training, hypothesized neurons were pathways of excitations responsible for psychological experiences. In fact, Freud's "Project for a Scientific Psychology" [7] reflected his vision by detailing how psychic phenomena in neurobiological terms included affect, consciousness, dreaming, memory, perceptions, self and symptom formation, just to name a few [8]. Freud [7] also believed that hormones in the brain influenced emotional and mental life, but was unsure of the specifics of their functioning. While Freud lacked the technology to further test his theories, he anticipated future discoveries in neurobiology and chemical properties would advance psychoanalysis [9].

And Freud was right. Modern scientific testing in the form of fMRIs, PET scans and EEGs have validated many of his concepts. For example, Julius Axelrod [10] discovered the neuronal-synaptic function of neurotransmitters of norepinephrine, epinephrine, and dopamine in the brain. And the role of additional neurotransmitters soon followed, including acetylcholine, serotonin, GABA, glutamate, orexin, and other neuropeptides [11]. While many neurobiological discoveries regarding brain and behavior have occurred, history shows that psychoanalysts have been, at best, cautious about combining medication with psychoanalysis [12].

In the late 1950s, when psychotropic medications were first developed, their use as an ancillary treatment was met with outright rejection by the psychoanalytic community. Analysts believed the deep and curative work in psychoanalysis needed to remain undisturbed, so the use of medication was considered an intrusion [13]. Some criticisms about inviting medication into the analytic treatment frame was that exploration of unconscious patterns, resistances, transferences, and other psychoanalytic concepts would be diluted or even derailed when medication was introduced to treatment [14]. Others voiced concern how the need for the analyst "to cure" the patient with medication might set up unexamined countertransference issues or activate rescue enactments, or the goal of eliminating psychological pain through the use of pharmacotherapy might be counterproductive for psychological growth [12].

But not all analysts felt medication was a disruption in the analytic frame [14,15]. When SSRI's were being introduced in the 1980's, more psychoanalysts embraced the possibility of using medication. Even Anna Freud expressed her support of using medication in analysis during her visit to the New York Psychoanalytic Institute - sharing how she'd used medication with depressed patients and found no obstructions in the analytic frame. Freud further expressed that using medication appeared to maintain analysis when her patients' untreated symptoms might otherwise have required hospitalization [13]. The medication boon of the 1990's and 2000's led to a plethora of studies showing how medication combined with psychotherapy was a viable evidenced-based treatment for many psychological disorders [16]. And while there are some who still hesitate to use medication in psychoanalysts, most analysts have evolved with the research, broadening their knowledge of pharmacotherapy.

As psychoanalysts, we believe mental disorders are the result of traumas and stressors inherent in the human condition. More specifically, we deem the structure of symptoms can be traced to maladaptive defensive operations and relational and attachment setbacks. Though we treat many patients without the use of medication, we need to advance our awareness of genetic testing for patients who need medication. While there is no current research or case studies on the use personalized medicine and psychoanalysis, Frank [17] reminds us how the next wave of significant change in psychoanalysis will involve greater integration of nonanalytic approaches. And this next wave, I believe, is personalized medicine.

## Treating Depression

Major depressive disorder (MDD) is one of the most common mental illnesses in the United States. According to the Center for Behavioral Health Statistics and Quality [18] the *Substance Abuse and Mental Health Services Administration* national survey reported over 16 million adults or 6.7% of the adult population have been diagnosed with depression. Depression also occurs in children, with 4% of preschoolers, 5% school aged children and 11.2% adolescents experiencing a diagnosable depressive disorder [19]. When it comes to MDD or Dysthymia, analysts use talk therapy to reduce symptoms. As previously mentioned, for some of our patients, psychotherapy alone will ease the symptoms of depression. But for many, the treatment plan will likely lead to a psychiatric consultation for medication.

Pharmacotherapy treatment for depression regulates neurobiology and the monoamine neurotransmitters serotonin (5HT), norepinephrine (NE), and dopamine (DA) in a series of neural circuits in the brain [20]. While there are over 20 medications approved by the FDA to treat depression, and many others recommended for off-label use, treatment failure with antidepressants commonly occurs in clinical practice [21]. Studies report upwards of 60% of patients fail to enter remission with a first antidepressant prescribed [22]. And up to 25% do not respond at all [23]. Inviting personalized medicine into the treatment plan when working with depressed patients can reduce the rate of medication

failure. It will also detect *response to treatment* -who will have a better, slower or a non-response to medication. Serretti [24] described a meta-analysis of the 5-HTTLPR gene promoter showed individuals with an L allele had a better response to SSRI medication than individuals with an S allele. Duprey [25] and Schosser, et al. [20] report mutations in the MTHFR gene leads to treatment resistant depression (TRD) and individuals with COMT gene polymorphisms have a 76% of being treatment resistant to medications. Gaining this information before starting medication will certainly streamline treatment plans, but can also set the stage for anticipating TRD and having alternative, complementary or experimental treatments outlined, explored and waiting to be accessed.

When working with patients who have depressive disorders, analysts witness the painful journey of terrible side effects. While we hope that dosing levels or time changes reduce these unpleasant experiences for patients, it's often a waiting game of "let's see". With pharmacogenomics, medications suited to a patient's genetics will mean less side effects, and as a secondary gain, greater medication compliance. And most importantly, no more prescribing in the dark and no more time lost in sessions waiting to see if medication reaches a therapeutic level [26].

Genetic testing for antidepressant medication can also help clinicians address aspects of psychological resistance more clearly. In the past, it was difficult to discern if poor recovery was a result of medication not working. Or if the dose was too low for therapeutic results. Or too high and side effects were undermining recovery. With precision medication, analyst and patient can work together to determine why treatment is flagging. It will be less about finding the right medication, because genetic testing has helped identify it - and more about the way medication is being managed. Is it because of missed doses? Or noncompliance? Or if the medication is being taken as prescribed, the work can look at developing insight into past traumas, patterns or other psychological resistance defenses.

## How pharmacogenetic testing works

There are many genetic labs that specialize in precision medicine, with more launching every year. Leading labs like *AlphaGenomix, AssuredRX, Genelex and GeneSight*, just to name a few, offer a variety of panels. These different personalized genetic testing options can evaluate medications for addiction, antibiotics, ADHD, cardiac, infectious diseases, oncology, psychiatric, psychotropic and other polypharmacy needs. When considering genetic testing for antidepressants, a full psychiatric genetic panel is recommended.

Generally speaking, the prescribing psychiatrist, or psychiatric nurse practitioner swabs the cheek of the patient, places it in the supplied sterile tube and then into a prepaid mailing packet. Enclosed along with the cheek swab is a completed medical, prescription history and signed order so that the lab can sequence each of the medications a patient is OR may be planning on taking. The turn-around is relatively fast, about a week or two for the results to come back in a written report. Once the results are in, the patient and the prescribing clinician are mailed hard copies of the report. While the genetic lingo and abbreviations may be intimidating to non-scientists, reports are written with color coded keys and with general explanations. Labs also offer customer and provider service assistance to go over results should further clarification be needed.

## Overview of genetic testing

Genetic studies report *Cytochrome p450* is responsible for metabolizing more than 80% of the medications people take and are most susceptible to individual gene variations [27]. Though *Cytochrome p450* testing involves aspects of biochemistry beyond the realm of this article, the take-away here is this genetic test assesses unique genes, alleles, and enzymes. More profound is the evidence that *Cytochrome p450* metabolism varies by gender and ethnicities, making a one-size-fits-all approach to medication outdated.

Pharmacogenomic testing offers many advantages. The first of which is to identify what kind of metabolism for medications a person possesses. According to Mrazek [28], there are four metabolizing categories: *poor, intermediate, normal and ultrarapid*.

- **Poor metabolizer (PM)** is a person whose metabolism takes in the medication very slowly, resulting in increased levels of the medicine in the bloodstream. This sluggish process causes significant side effects, and poses toxicity risks such as serotonin syndrome-a potentially life-threatening condition caused by toxic levels of serotonin. If you're a poor metabolizer, you not only have the hardship of experiencing side effects and toxicity, you also continue to have depressive symptoms.
- **Intermediate metabolizer (IM)** is a person whose metabolism of a medication occurs at a slower rate than normal. People in this category experience side effects and mild toxicity but not as intensely as do poor metabolizers. As you might expect, medication success is guarded in this category. You notice some symptom relief, but it won't be substantial.
- **Normal metabolizers (NM)** have an average expected range for metabolism. Herein, you absorb medication effectively and are able to experience symptom relief with little or no side effects. A person who has a normal metabolism can take medications at recommended FDA dosages.
- **Ultrarapid metabolizers (UM)** quickly process medication, rendering drug treatment virtually ineffec-

tive. Because your genetic metabolism synthesizes the medication too fast, you cannot experience its therapeutic effects. If you're an ultrarapid metabolizer, you feel no symptom relief whatsoever.

The second component *Cytochrome p450* testing offers is to detect optimal dosages for antidepressants, which helps find a therapeutic level more quickly for patients. The prescribing physician or nurse practitioner will adjust a target-specific dose of the recommended medication based on the patient's metabolizing category. No more guessing in the dark. Or starting low and increasing over time, hoping to find the sweet spot dose.

Another advantage is that genetic testing will determine how the antidepressant medication will affect a patient, and evaluate if there's at risk for **Adverse Drug Reactions (ADRs)**. Adverse drug reactions cost an estimated $177 billion each year, with an estimated 7,000 outpatient deaths, and more than 2 million ADRs and occur annually in hospitals per year [29]. Mild ADRs have a long history of being associated with antidepressant non-compliance, and for biasing patients to try newer or different medications [30]. Using personalized medication significantly diminishes the rate of ADRs, providing patients a level of confidence taking medication that heretofore is unprecedented.

A fourth benefit of this testing looks at the intermix of more than one medication - and how the combination will work with a patient's genetic makeup. So, if your patient is taking other medications in addition to an antidepressant, testing will provide prescribing recommendations about *each* of the drugs.

The final, and perhaps greatest advantage, is that genetic testing of antidepressants metabolism hastens the success rate for remission. Many who work with patients who are depressed have witnessed the weeks, months and even years for patient's to find the right medication. As Leckband [4] remind us:

"If one were to follow standard guidelines, allowing each medication trial for two months before treatment resistance is declared, and one were to try at least three selective serotonin reuptake inhibitors (SSRIs) and three non-SSRIs before moving to augmentation strategies, the patient would spend one year in monotherapy medication trials alone. If each of the antidepressant trials were augmented with two different agents, an additional two years would be spent in augmentation trials (p. 237)".

## Case Study

Carly was 60-years-old when she entered my office for her first session. This was not, however, her first go-round in psychotherapy. For over 40 years, she'd been in treatment with numerous therapists to address a long standing depression. Carly reported being in different kinds of therapies: behavioral, cognitive and psychodynamic psychotherapies for decades at a time. While each modality offered support, none alleviated her depressive symptoms. She also reported being on many different kinds of medications through the decades, some providing mild improvements, but with terrible side effects. Other cocktail mixes prescribed included mood stabilizers, MAOs or SSRi's that left her dulled and sluggish. She stayed on these prescriptions for many years, but ultimately would stop and seek something new to help ease symptoms.

Carly and I began working three times a week in analysis. Over the course of our first month, she painted a picture of being in a haze of depression most of her married adult life, with it worsening after the birth of her daughter. She was unable to hold a job outside of the home, take care of the house and parenting was a great challenge. Carly's husband was in the medical field, and worked a busy practice. At times, he was supportive and accepted the depths of her illness, while at other times, he'd wonder if she wasn't trying hard enough to get better. And worse, that she wasn't really depressed at all.

Carly had few friends and as her daughter became school age would find herself lost in the fog of negative thinking, feelings of despair and motor slowness. As time passed, Carly's husband became less sensitive to her emotional and physical needs and convinced Carly that she wasn't depressed, but rather willfully lazy. And because he was a health provider, Carly began to believe she wasn't living with an illness, but rather a limited way of life that was somehow self-imposed. That she, herself, was creating this dismal and colorless existence. Carly wondered if there were unconscious reasons for her chronic despair, or psychological resistances that needed to be explored. So, she made an appointment with me, a psychoanalyst, to pursue the journey of exploring her internal life.

When Carly entered treatment with me, she was not on any medications and was slipping deeper into a depression. Carly was, at best, able to dress, drive and get to sessions. But at worst, unable to think clearly, consistently self-care or feel hopeful about her life. As I got to know Carly, she impressed as bright and expressive. Yet her voice and tone were soft and thin. She was always well dressed, but a physical frailty was easily observable. Her gait was slow, as were her mannerisms. There was a wilting in her face and body, and a dullness in her eyes.

Carly shared in sessions that she enjoyed doing very little in life, and that her world was very small. She was able to engage in passive activities, like reading or keeping up with the news of the world by watching television, but when it came to more active kinds of self-care (eating, sleeping, exercising), family care (cleaning, cooking, shopping, scheduling, parenting) or purposeful life experiences (working, paying bills, socializing), she felt adrift and untethered. When I asked about any suicidal

thinking, Carly reported wanting to die many times in her life, but never felt the urge to act on such impulses.

"*It took too much of the little I had to act on things*," she once said.

By the end of the first month of analysis, Carly's symptoms only minimally improved. I noted that a lot of our session work was structured around helping her finish her thoughts or put words to feelings because her concentration was poor. The ability to investigate early traumas, transferences, and defensive patterns was challenging because Carly was so limited by her depressive symptoms. My countertransference reactions varied from feeling bored, restless and frustrated to worried and panicked about the depths of her illness. It was difficult to stay in the moment with Carly, but exploring these themes helped me understand how her loved ones oscillated between connection and disconnection with her. My need to "fix" or "help" was deeply felt a great deal during sessions, and it took work for me to linger in the painful symptoms along with Carly. But I did, and so did she. But the sessions were fixed and stagnant. And soon thereafter, Carly reflected that returning to medication was important. And I agreed.

During the next month, I introduced the idea of personalized medications. It was a new technology that was available, but Carly was not familiar with it at all. As this was a treatment-directive on my part, I suggested she read more about it if she was interested. Several sessions later Carly wanted to discuss how personalized medicine might be used in treatment. We spent several sessions considering the spectrum of possibilities genetic testing might offer. What it would mean if genetic testing yielded nothing to improve emotional functioning. What might be revealed if something significant was discovered. We also addressed Carly transferences, which at the beginning of sessions were moderate and positive, but had now become quite over- idealized once personalized medicine entered the treatment frame.

We spent many sessions exploring transference-focused themes and worked toward neutralizing the reverence. I shared how this technology was something I suggested to other patients. How personalized medicine was slow in making its way into other health professions - and that's why many aren't aware. I also examined my own countertransference to ensure that objectivity wasn't lost and that I wasn't compartmentalizing my own issues of wanting to be "a fixer".

Before the end of the second month of analysis, Carly said she scheduled an appointment with a new psychiatrist who utilized pharmacogenomic testing. It took 10 days to get a report back from the genetic lab once the psychiatrist conducted the test and Carly's pharmacogenomic results were life changing.

Four significant markers were detected. First, Carly's 5-HTT phenotype revealed difficulties with serotonin transporter expression, which lead to higher levels of side effects and adverse reactions with SSRI's. No wonder she felt terrible on such medications and eventually stopped taking them. Second, Carly also obtained High Activity in MTHFR gene. And third, a High Activity with COMT phenotypes was discovered. The MTHFR and COMT polymorphisms indicated poor remission from depression and treatment resistance. Finally, Carly was a slow metabolizer, which meant she needed higher than usual doses of the right medication to see results. Genetic testing showed that Carly had long been prescribed medications that did not suit her genetic needs.

These findings lead Carly's new psychiatrist to prescribe an SNRI, Pristiq. Within two months and some dose adjustments, she was feeling moderately better. Something she hadn't experienced in decades. Furthermore, accommodations were made through Carly's insurance company to cover rTMS (repetitive transcranial magnetic stimulation) due to her Treatment Resistant Depression genetic makeup, which offered additional mood enhancing benefits. On the SSNI and the rTMS, the heavy haze of her depression lifted, and we were finally able to journey deeper into the layers of her life. Carly's appearance also shifted. Her eyes were brighter, her face and body pulsing with purpose and interest. Her sense of humor took front and center as did a determined mindfulness to reclaim her life. She became more active at home and slowly created a social life both for herself, and as a couple. Moving from a passive, dim, shadowy existence to an active person took some of her family members by surprise. But, perhaps the most important finding from genetic testing was that Carly was not consciously choosing despair, inertia and disconnection. The idea of being *lazy* or *not trying hard enough* was put to rest.

## Summary

As psychoanalysts, we know that listening to our patients' narratives helps them make sense of their life and their symptoms [31]. But what if a patient's life narrative is unduly skewed by genetic anomalies that cloud realization? Or by neurobiology that heretofore systematically impedes recovery? As Sandberg [32] asked, how does being pharmacologically informed influence our analytic listening?

Incorporating pharmacogenomic testing for depression in this case showed how misleading it was to consider resistance - or other psychic defenses as causal for Carly's long-standing depression. Personalized medication lead to significant symptom relief, which resulted in a deepening of her subjective states and greater understanding of herself and her life. For Carly, genetic testing allowed the psychoanalytic work to bring newfound remembering, repeating and working through [33].

Carly continues in psychoanalysis, learning to find ways to accept the sorrow of what she's termed "the

lost decades". She has emerged from the depths of her depression in ways that surprise, frighten and challenge - as most new experiences do for us all. She's mindful about taking medication as prescribed and attends rTMS regularly. The use of genetic testing in Carly's case was as vital as a detailed inquiry, as exploring defenses, deepening insight, detecting patterns and ways of thinking, or any of the essential tools analysts use in treatment.

Personalized medicine offers a promise of understanding - of hope and of healing for patients. And for us, as analysts, it becomes a tool for deeply meaningful treatment.

## Compliance with Ethical Standards

### Conflict of Interest

Author Deborah Serani, Psy.D., declares no conflict of interest. No funding was obtained for this article.

### Ethical Approval

This article does not contain any studies with human participants or animals performed by the author.

Informed consent: Informed consent was obtained from the individual included in the case study.

## References


1. Hood L, Rowen L (2013) The human genome project: Big science transforms biology and medicine. Genome Med 5: 79.
2. Carroll J (2007) Biogenetic tests emerge from their chrysalis. Biotechnol Healthc 4: 37-44.
3. Patrinos GP (2018) Population pharmacogenomics: Impact on public health and drug development. Pharmacogenomics 19: 3-6.
4. Leckband SG (2014) Pharmacogenomic testing for treatment resistant depression. Mental Health Clinician 4: 236-239.
5. Offitt K (2011) Personalized medicine: New genomics, old lessons. Hum Genet 130: 3-14.
6. Haga SB, Barry WT, Mills R, Ginsburg GS, Svetkey L, et al. (2013) Public knowledge of and attitudes toward genetics and genetic testing. Genetic Testing Mol Biomarkers 17: 327-335.
7. Freud S (1895) Project for a scientific psychology. In: Strachey J, The standard edition of the complete psychological works of sigmund freud. Hogarth Press, London, 1: 283-397.
8. Glucksman ML (2016) Freud's "project": The mind-brain connection revisited. Psychodyn Psychiatry 44: 69-90.
9. Norman WC, Bluestone H (1986) The use of pharmacotherapy in psychoanalytic treatment. Contemporary Psychoanalysis 22: 218-223.
10. Axelrod J (1957) O-methylation of epinephrine and other catechols in vitro and in vivo. Science 126: 400-401.
11. Eric R Kandel, James H Schwartz, Thomas M Jessell, Steven A Siegelbaum, Hudspeth AJ, et al. (2012) Principles of Neural Science. McGraw-Hill, New York.
12. Riccio DJ (2011) Medicating patients in psychoanalytic therapy: Implications for introjection, transference, and countertransference. Am J Psychoanal 71: 338-351.
13. Knowlton L (1997) Psychoanalysis and pharmacotherapy - Incompatible or synergistic? Psychiatric Times 14: 1-2.
14. Busch FN, Malin BD (1998) Combining psychopharmacology, psychotherapy and psychoanalysis. Psychiatric Times 15: 1-2.
15. Roose SP, Johannet CM (1998) Medication and psychoanalysis. Treatments in conflict. Psychoanalytic Inquiry 18: 606-620.
16. Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, et al. (2013) The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: A meta-analysis of direct comparisons. World Psychiatry 12: 137-148.
17. Frank KA (2013) Psychoanalysis and the 21st Century: A critique and a vision. Psychoanalytic Perspectives 10: 300-334.
18. Center for Behavioral Health Statistics and Quality (2017) 2016 National survey on drug use and health: Methodological summary and definitions. Substance Abuse and Mental Health Services Administration, Rockville, USA.
19. Serani D (2013) Depression and your child: A guide for parents and caregivers. Roman & Littlefield Publishing Group, Lanham, USA.
20. Schosser A, Calati R, Serretti A, Massat I, Kocabas NA, et al. (2012) The impact of COMT gene polymorphisms on suicidality in treatment resistant major depressive disorder. Eur Neuropsychopharmacology 22: 259-266.
21. Leuchter AF, Cook IA, Hamilton SP, Narr KL, Toga A, et al. (2010) Biomarkers to predict antidepressant response. Curr Psychiatry Rep 12: 553-556.
22. Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, et. al. (2006) Medication augmentation after the failure of SSRIs for depression. N Engl J Med 354: 1243-1252.
23. Al-Harbi KS (2012) Treatment-resistant depression: Therapeutic trends, challenges, and future directions. Patient Prefer and Adherence 6: 369-388.
24. Serretti A, Kato M, De Ronchi D, Kinoshita T (2007) Meta-analysis of serotonin transporter gene promoter polymorphism 5 HTTLPR association with selective serotonin reuptake inhibitor efficacy in depressed patients. Mol Psychiatry 12: 247-257.
25. Duprey R (2016) MTHFR gene polymorphism for treatment-resistant depression: Prevalence and treatment recommendations. Neuropsychiatry 6: 43-46.
26. Serretti A (2018) The present and future of precision medicine in psychiatry: Focus on clinical psychopharmacology of antidepressants. Clin Psychopharmacol Neurosci 16: 1-6.
27. Matchar DB, Thaku M (2007) Is genetic testing for Cytochrome P450 polymorphisms ready for implementation? Am Fam Physician 76: 348-351.
28. Mrazek DA (2010) Psychiatric Pharmacogenomics. Oxford University Press, New York.
29. Shepherd G, Mohorn P, Yacoub K, May DW (2012) Adverse drug reaction deaths reported in the United States. Vital statistics, 1999-2006. Ann Pharmacother 46: 169-175.
30. Allen JG (2002) Coping with the catch-22s of depression: A guide for educating patients. Bull Menninger Clin 66: 103-144.
31. Volkan VD (2010) Psychoanalytic technique expanded: A

textbook on psychoanalytic treatment. OA Press, London & Istanbul.

32. Sandberg LS (1998) Analytic listening and the act of prescribing medication. Psychoanalytic Inquiry 18: 621-638.

33. Freud S (1914a) Remembering, repeating and working-through. In: Strachey J, The standard edition of the complete psychological works of sigmund freud. Hogarth Press, London, 6: 147-156.