

IMPACT OF PSYCHIATRIC MEDICINE, PHARMACOTHERAPY, AND DRUG METABOLISM ON DEPRESSION AND EMOTIONAL REGULATION IN ADOLESCENTS

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ABSTRACT

Background: Adolescence is this kind of dynamic neurodevelopmental phase, where neural circuits in charge of emotion control, reward processing, executive regulation, stress responsivity and social cognition start maturing a lot. During this time, depression often shows up together with emotional dysregulation, sleep problems, harder thinking, and reduced psychosocial functioning. This review sort of brings together psychological, neurobiological, psychiatric, pharmacological and pharmaco-metabolic lenses, to look at how adolescent depression links to emotional regulation, and there's a special focus on antidepressant pharmacotherapy plus cytochrome P450 mediated drug metabolism.

Method: This kind of qualitative narrative review goes through current literature that talks about adolescent depression and emotional regulation, neurodevelopment and the prefrontal limbic circuitry, reward processing and also hypothalamic-pituitary-adrenal-axis activity. It also touches inflammation, neuroplasticity, sleep, and then moves into antidepressant pharmacotherapy, including pharmacokinetics, pharmacodynamics, and pharmacogenetics. There is, in a way, special attention on CYP2C19 and CYP2D6, since they're already known to be tied in with the metabolism of several antidepressants. Adolescent depression seems to come about from a messy set of interactions between developmental, psychological, environmental, and biological processes, not like one lone neurochemical glitch.

Result & Conclusion: Emotional regulation might be a key clinical phenotype, sort of linking altered affective processing, with the later depressive symptoms too. At the same time, antidepressant exposure isn't consistent across individuals, and variation in CYP2C19 and CYP2D6 genetics could help explain differences in pharmacokinetics, and tolerability. But, the developmental stage, co-prescribed drugs, how well someone sticks to the regimen, the disease characteristics and the surrounding environment, all steer the treatment response. So, integrating emotional regulation and neurobiology with pharmacokinetics and pharmacogenetics might end up giving this more complete framework for figuring out why people respond differently. Still, the evidence in pediatrics is kind of less developed compared with adults, and genotype shouldn't be read as a self-standing cause of antidepressant efficacy.

KEYWORDS: Adolescent Depression; Emotional regulation; Neurobiology; Pharmacotherapy; Antidepressants; Drug Metabolism; CYP2C19; CYP2D6

1. INTRODUCTION

Adolescence is kind of a distinctive phase of human growth, with all this biological, psychological and social shifting going on at the same time. During pubertal maturation, the brain keeps developing too, especially cortical and subcortical neural systems tied to emotional processing, reward signaling, executive control, decision making and social cognition [1-4]. This whole developmental mixture can help adaptive maturing, but it may also bring in windows of greater vulnerability to psychopathology, you know.

Depressive disorders that show up during adolescence are extra important, because they can disrupt education, interpersonal ties, sleep patterns, drive, cognitive functioning and even later developmental paths [5-8]. Adolescent depression might show up as ongoing sadness and anhedonia, but irritability, heightened emotional reactivity, social withdrawal, problems with attention and concentration, sleep disturbance and lowered motivation can be just as noticeable [5,6].

Contemporary models of depression lately describe it as something like a tangle between neural circuits, neurotransmission, neuroendocrine activity, inflammation, neuroplasticity, thinking patterns, emotion regulation and environmental stressors, not just some straightforward shortage of one neurotransmitter [9-13].

Emotional regulation seems especially connected with this view. Emotion regulation, in general, includes the processes by which people shape the intensity, how long, how they interpret, and even how they express emotional experiences [14]. In adolescence, those regulatory skills keep developing, meanwhile affective signals

and reward systems are getting reorganized in a pretty big way [2,3,15]. So problems when it comes to regulating negative affect could end up feeding rumination, impulsive reactions, avoidance, friction in relationships and, all in all, a higher risk for depressive conditions.

At the same time, pharmacological treatment adds yet another layer of biological heterogeneity. Adolescents on the “same” antidepressant, even if the doses look similar, may still end up with different plasma levels, different benefits, and different adverse reactions. Variability like this can come from differences in absorption, distribution, metabolism, and elimination [16,17].

Cytochrome P450 enzymes, especially CYP2C19 and CYP2D6, take part in the metabolism of multiple psychotropic medications. Genetic variation within these enzymes can result in distinct metabolizer phenotypes and, in turn, affect exposure to particular antidepressants [18-21].

The clinical weight of pharmacogenetics has grown as organizations developed guidance, for example the Clinical Pharmacogenetics Implementation Consortium (CPIC). The CPIC advice now contains suggestions that involve CYP2D6, CYP2C19 and also CYP2B6 for certain serotonin-reuptake inhibitors [20]. Still, when you try to bring pharmacogenetic results into pediatric psychiatry you need extra caution, because developmental pharmacology, plus adolescent -focused clinical evidence, is still rather less extensive than in adults [21,22].

So, the aim of this qualitative review is to bring together psychological, developmental neuroscience, psychiatry, pharmacology, pharmacokinetics, and drug-metabolism perspectives on adolescent depression and emotional regulation. Instead of treating drug metabolism as a root reason for depression, the review frames it mainly as a possible driver of differences in pharmacological exposure and in how people respond to treatment, after depression has already emerged.

2. ADOLESCENT NEURODEVELOPMENT AND VULNERABILITY TO DEPRESSION

2.1. Neurodevelopment during adolescence

Adolescent brain development keeps going, with structural and functional maturation across distributed neural networks. Even if a lot of change happens during childhood, the prefrontal cortex and its regulatory systems keep developing through adolescence, and also into early adulthood [1-4].

The prefrontal cortex helps with executive functioning, cognitive flexibility, inhibition, choices, and emotion regulation. Meanwhile, limbic and reward-related systems show key developmental shifts too. So the back and forth between these systems really matters if you want to understand adolescent affective functioning [2,3].

It's a mistake to treat adolescence as only a stretch of weak cognitive control. Rather, adolescence is a stage of development with heightened neural plasticity, shifting reward sensitivity, and ongoing fine-tuning of regulatory circuitry [3,15]. Because of this, young people may become more tuned to social scrutiny, stressors and reward-linked situations.

2.2. Prefrontal-limbic interactions

Emotion regulation seems to need a kind of coordination between cortical regulatory zones, and the subcortical parts that handle emotional salience, or at least they do in many models. The amygdala, helps with detection and processing of stimuli that really stand out emotionally, while prefrontal areas along with the anterior cingulate regions are involved in judging, reducing, and tuning emotional responses [23-26].

In adolescence, the connections between these systems are still maturing, and they don't just “lock in” right away. So depression might reflect disturbances in the working together of these networks, instead of being only isolated oddities inside one single structure [27-30].

Functional neuroimaging work has found that in depressive disorders, there are changes in activity and in connectivity touching the default mode network, the salience network, executive control systems, and also front limbic circuitry [27-31]. Taken together, these findings back a network level understanding of adolescent depression, rather than thinking everything is driven by one node.

3. EMOTIONAL REGULATION AND ADOLESCENT DEPRESSION

3.1. Conceptualizing emotional regulation

Emotion regulation is about the processes whereby people, kind of adjust their emotional experiences and reactions, not just in one moment but over time [14].

Gross's process model highlights a number of spots where emotional responses can be tuned, like situation selection, situation modification, attentional deployment, cognitive change and also response modulation [14]. So emotional regulation can mean more emotional reactivity than needed, trouble letting go of negative affect, less useful attentional habits or narrow patterns of focus, limited cognitive reappraisal, impulsive emotional reactions or ongoing rumination, that doesn't really quit. Taken together, these processes matter a lot for adolescent depression.

3.2. Emotional regulation as a developmental process

The skill to regulate emotions grows step by step, really across childhood and into adolescence. As cognitive control systems mature, they get better at modulating emotional reactions, plus social happenings and the surrounding environment also shape the kinds of regulatory strategies people use [15,32]. Because of that, the adolescent stage ends up being marked by a lot of room for positive, adaptive growth and also for fragility, at the same time. When the surroundings are stressful, they can team up with regulatory systems that are immature or still in the process of developing, and that may lead to a longer lasting negative affect.

3.3. Emotion regulation and depressive symptoms

Having difficulties with emotion regulation, has been tied to depression, anxiety and other types of psychopathology [33-35] kind of broadly. Some maladaptive strategies , like rumination, suppression and avoidance might keep those negative emotional states going. On the other hand adaptive strategies such as cognitive reappraisal, acceptance and problem solving can ease emotional distress.

Also, emotional regulation should not be treated as the same thing as depression. Instead, it may act like a transdiagnostic process, helping to shape how severe, persistent, or how clearly expressed depressive symptoms end up being.

4. NEURAL CIRCUITRY OF EMOTIONAL REGULATION

4.1. Amygdala

The amygdala plays a key role in the detection, and processing of emotionally noticeable stimuli, like it kind of “sorts” what matters. Altered amygdala activity and connectivity has been reported in depression, but the actual direction and the clinical meaning of these findings really can vary between studies [24,36], so results are not always pointing the same way. In adolescents, developmental changes in amygdala–prefrontal interactions might shape emotional reactivity, regulation too, more than people first expect.

4.2. Prefrontal cortex

Some prefrontal regions seem to help with control and cognitive regulation, like there’s this overall steering aspect. For example the dorsolateral prefrontal cortex gets linked to cognitive control and working memory activities, while ventromedial together with orbitofrontal areas are thought to support things like valuation , emotional processing and the actual decision-making [23,25]. When the efficiency of these regulatory setups goes down, it might make it harder to disengage from unpleasant thoughts , or to rework the way emotions are interpreted , so the negative framing sort of sticks.

4.3. Anterior cingulate cortex

The anterior cingulate cortex kind of helps with conflict monitoring, it also plays a role in affective processing and regulation , in a way. Subgenual anterior cingulate abnormalities have been especially studied when it comes to mood disorders [37, 38] , though. Changes in this part of the brain may be linked to a weirdly abnormal integration of emotional plus cognitive information.

4.4. Large-scale neural networks

Nowadays neuroimaging research, keeps showing how distributed networks matter more and more. You know the default mode network, it gets tied to self talking stuff and to cognition that is turned inward. Then there is the salience network, it helps in singling out what is behaviorally important, stimuli in particular. And the executive-control network supports goal driven cognition, like you’re steering toward something. Depression has been linked with odd interactions, between these systems [27-31] , in multiple studies. This whole network framing is kind of handy for emotional dysregulation too, because emotional regulation can’t really be pinned on just one brain region.

5 . STRESS, HPA-AXIS FUNCTION AND DEPRESSION

5.1. HPA-axis activation

The hypothalamic–pituitary–adrenal (HPA) axis kind of acts like a big physiological corridor linking psychological stress with endocrine responses, in a more or less straight line. When stress hits, hypothalamic corticotropin-releasing hormone gets activated, then that moves on to adrenocorticotrophic hormone release and eventually adrenal cortisol production follows. If this whole system stays off-balance for a long time, it has been tied to depressive disorders [42-44]. Adolescence might matter more than people think, since the HPA axis experiences developmental tuning while adolescents deal with more and more intricate social plus academic stressors all at once, which can be pretty intense.

5.2. Chronic stress and emotional regulation

Chronic stress might mess with emotional regulation , kind through changes in prefrontal–limbic wiring, plus effects on how the hippocampus works , neuroplasticity, and also inflammatory pathways. So in a way stress offers a kind of plausible connection between what happens in someone’s surroundings and a biological vulnerability that is already there. Still , stress exposure doesn’t always lead straight to depression or anything like that. Outcomes vary because of individual differences, including resilience, social backing, coping strategies, genetics, and the underlying neurobiology, overall.

6. NEUROINFLAMMATION AND ADOLESCENT DEPRESSION

Stress related inflammatory signaling might feed into emotional processing, and in depression research inflammatory mechanisms keep getting more attention, almost like everyone is looking that way now. Cytokines plus inflammatory signaling pathways can affect neurotransmission, neuroendocrine functioning, sleep, motivation and neural plasticity [45-48].

In children and adolescents, there’s evidence for mild inflammatory shifts in a small subset of people with depression, but the data still looks pretty mixed, a bit patchy [49]. So inflammatory mechanisms should be treated as possible contributors, not as universal biomarkers or something that fits everyone. One key implication is that depression could involve back and forth interactions between psychological stress and

immune functioning. That shows up in fatigue and sleep, while sleep disruption and behavioral changes might also nudge inflammatory processes along. This reciprocal picture may be especially relevant for adolescents.

7. NEUROPLASTICITY AND BDNF

Neuroplasticity means the ability of neural systems to alter themselves structurally and functionally, as development goes on, through experience, and due to those environmental kinds of pressures. The Brain-derived neurotrophic factor, or BDNF, gets tied into neuronal survival, synaptic performance and those plasticity related shifts. When stress brings about alterations in neuroplasticity, it's been linked with depression, and antidepressant treatment can also modulate neuroplastic processes [50-52].

This whole perspective has helped the field move away from explanations that are only centered on neurotransmitters, and more toward broader mechanisms. For adolescents, neuroplasticity is especially important because major neural remodeling keeps happening during this developmental window. Still, BDNF levels measured in the periphery can't just be taken as if they're direct reflections of brain BDNF activity, not automatically, not straightforwardly.

8. PHARMACOTHERAPY OF ADOLESCENT DEPRESSION

8.1. Role of antidepressants

Psychological therapy is still, somehow an important part of how we handle adolescent depression management, overall. Depending on how severe the clinical picture looks, and on the surrounding situation, pharmacotherapy might be used by itself, or teamed up with psychological interventions. Selective serotonin reuptake inhibitors, aka SSRIs, make up an important pharmacological group for adolescent depression.

Clinical findings suggest that some SSRIs, especially fluoxetine, have shown efficacy for pediatric depression [56-59]. Even so, giving antidepressants to adolescents needs careful clinical follow up, since both the treatment response and the unwanted effects can differ from one person to another.

9. PHARMACOKINETICS AND ANTIDEPRESSANT EXPOSURE

Pharmacokinetics is the processes of absorption, distribution, metabolism and elimination. Drug metabolism can significantly affect systemic exposure.

The relationship can be noticed as:

Dose → absorption → distribution → metabolism → elimination → systemic exposure → tissue exposure → pharmacological effect

The same advised dose does not generally show the result as the same exposure in every individual. This is specifically important for medications with substantial hepatic metabolism.

9.1. Developmental pharmacokinetics

Teenagers are sort of different from adults in their body build, organ coming online, endocrine function, and also in general physical growth. So, because of that pediatric and adolescent pharmacokinetics can't always be figured out just by scaling adult doses, like it's a straightforward proportional thing. As people mature, developmental changes can shift enzyme activity, hepatic clearance and renal elimination results. That's really what shows why it matters to account for age and developmental phase together with genetic background too.

10. CYP2C19 AND ANTIDEPRESSANT METABOLISM

CYP2C19 is kind of an important hepatic drug metabolizing enzyme, and it plays a role in how several antidepressants get metabolized. You can picture the relevant substrates as including citalopram, escitalopram, and sertraline, even if the relative weight of CYP2C19 kind of shifts a little between them. And then, genetic variants in CYP2C19 can lead to different metabolizer phenotypes, sort of like different "speed modes" in real life. In general, people may be sorted into categories such as poor metabolizers, intermediate metabolizers, normal metabolizers, or ultrarapid metabolizers.

So the clinical implication is basically this: the same administered dose can still end up producing different concentrations from person to person, yes. The CPIC recommendations bring the CYP2C19 phenotype into the prescribing workflow for selected SSRIs [20]. Even so, the genotype to exposure relationship doesn't really mean that genotype by itself entirely controls the clinical response.

11. CYP2D6 AND ANTIDEPRESSANT METABOLISM

CYP2D6 is a kind of the most extensively studied pharmacogenetic enzymes in psychopharmacology, in general. It's tied to the breakdown of numerous medications, including a few antidepressants. Genetic variation in CYP2D6 then brings about pretty noticeable differences between people in enzyme activity [18,60-63], which is why individuals don't respond in the same way. So patients can end up with a poor, intermediate, usual, or even ultrarapid metabolizer phenotype. If someone is a poor metabolizer they might wind up with higher exposure to a medication that is largely handled via CYP2D6, and that can increase the likelihood of adverse events. On the other hand, ultrarapid metabolism can reduce exposure for certain substrates which sounds straightforward but it isn't the whole story. Even then, how you interpret it really depends on the particular drug, because not every antidepressant leans equally on CYP2D6.

12 . CYP ENZYMES, DRUG-DRUG INTERACTIONS AND PHENOCOPYING

Genotype does not fully, or really, decide metabolic phenotype. So even if someone is genetically expected to show normal CYP2D6 activity they can still have a changed metabolism because of some other drug that inhibits CYP2D6.

Because of that, clinical pharmacology needs to take into account , not only one thing but: Genotype + concomitant medication + physiological status + developmental stage = the metabolic phenotype that you actually see. This ends up being a key weakness of simplistic pharmacogenetic models. Also, drug–drug interactions can shift drug exposure in ways that matter more clinically than genetic variation in certain situations. So medication history is still essential, even when pharmacogenetic data is available.

13. PHARMACOGENETICS AND ANTIDEPRESSANT RESPONSE

Pharmacogenetics looks at how inherited genetic differences, help explain why people respond differently to medications, sometimes its a big part, sometimes its subtle. In the context of antidepressants, CYP2C19 and CYP2D6 have gotten a lot of attention since they shape pharmacokinetics pretty directly.

Still, treatment response isnt just one thing—it is multidimensional outcome, depends on more than metabolism alone. It turns on: pharmacokinetics + pharmacodynamics + disease phenotype + psychological factors + surroundings + adherence. So, pharmacogenetics really needs to be seen as one piece inside precision psychiatry, not like a single, standalone predictor that tells everything by itself.

14. PEDIATRIC AND ADOLESCENT PHARMACOGENETICS

Bringing pharmacogenetics over into adolescent psychiatry needs some particular caution, like a lot. A systematic review on antidepressant pharmacogenetics in children , and young adults found evidence tied to CYP2C19, CYP2D6 and several other genes but still stressed how limited the replication is and how heterogeneous the pediatric data looks [64]. More recent pediatric discussions say something very similar too, namely that CYP2C19 , and CYP2D6 could offer helpful insight for certain medications while also warning against wide, sweeping assumptions about what clinical outcomes will happen [21,22]. That difference really matters because there is a pharmacogenetic association , does not automatically imply that routine genetic testing will improve outcomes for every single adolescent.

For clinical usefulness, you still need proof that testing actually shifts prescribing choices, and then leads to better efficacy, improved tolerability or enhanced safety.

15. PHARMACODYNAMICS VERSUS PHARMACOKINETICS

Pharmacokinetics is kind of about what the body ends up doing with the drug, more or less. But Pharmacodynamics is about what the drug does to the body, not the reverse. CYP2C19 together with CYP2D6 mostly shape pharmacokinetics, in practice.

But the real therapeutic response to an antidepressant also depends on pharmacodynamic happenings, like serotonin reuptake transport, receptor signaling, alterations in neural plasticity and downstream circuit stuff. So even if the drug exposure is “normal” that doesn’t automatically turn into a treatment win, not always. Similarly, if exposure is altered, or drug levels are shifted, it doesn’t automatically mean the therapy will fail either, ok. This divide matters a lot when you’re looking at pharmacogenetic results and you’re trying to make sense of what they actually imply.

16. EMOTIONAL REGULATION AS A POTENTIAL TREATMENT PHENOTYPE

An important interdisciplinary proposition is that emotional regulation may function as a clinically useful phenotype within adolescent depression. Depression is diagnostically heterogeneous.

Two adolescents may fulfill the same diagnostic criteria while presenting with different combinations of: anhedonia; irritability; rumination; anxiety; emotional reactivity; sleep disturbance; cognitive impairment; and social withdrawal.

Emotional regulation measures could therefore, sorta complement categorical psychiatric diagnoses ,and that seems useful. Future studies might look into whether specific emotional- regulation profiles actually interact with the pharmacokinetic characteristics. Like, researchers could examine whether the CYP2C19 phenotype predicts antidepressant exposure while the emotional-regulation phenotype predicts symptom change, kind of independently. Altogether ,these relationships are only hypotheses for later research, not established clinical conclusions.

17. ROLE OF CYP2C19 AND CYP2D6 IN PRECISION PSYCHIATRY

Precision psychiatry seeks to move beyond a one-size-fits-all treatment model. In pharmacotherapy, precision approaches may incorporate: clinical phenotype; previous treatment response; age; comorbidity; concomitant medications; pharmacokinetics; pharmacogenetics; and patient preferences.

CYP2C19 and CYP2D6 represent kinda useful parts in this model, at least potentially. CPIC guideline offers genotype-informed recommendations for a few serotonin re-uptake inhibitors, which is pretty handy [20]. Still, in real clinical use, implementation should be steered by validated drug-gene relationships not by wide-ranging

commercial claims , or stuff like that. Just because a genetic test exists doesn't automatically mean there is clinical utility.

18. ETHICAL CONSIDERATIONS IN ADOLESCENT PHARMACOGENETICS

Pharmacogenetic testing in adolescents brings up ethical topics around privacy, consent, and the way results are interpreted, not just one thing. Genetic information can stay useful, or at least relevant, for someone across their lifetime. At the same time, adolescents are still gaining autonomy while parents or guardians often stay involved in medical choices, which makes everything feel a bit more complicated. Because of that, any genetic findings should be shared carefully, and not in an overly direct way.

A CYP2C19 poor-metabolizer outcome, for example, should not be presented like a sure sign, that the adolescent will necessarily run into adverse effects. Instead, it needs to be described as data that may shift the likelihood of certain pharmacokinetic outcomes for selected medications. Getting away from genetic determinism is essential, basically you want to avoid treating the result as destiny.

19. POTENTIAL CLINICAL IMPLICATIONS

- To start with clinicians ought to see that the treatment response is basically heterogeneous, by nature. Also the medication history , along with possible drug drug interactions should be reviewed with care. Then, psychological symptoms should not be split away from pharmacological issues, they are kind of tangled together in real life.
- After that, CYP2C19 and CYP2D6 data might be used when it actually fits the case and is backed by validated clinical guidelines. Further, choices about treatment should stay individualized , not standardized in a rigid way.
- And of course, psychological interventions should keep a central role even if medication is involved. Finally , sleep along with environmental stress should be evaluated, because they can nudge emotional regulation and treatment outcomes, in ways that are easy to overlook.

20. CONCLUSION

Adolescent depression is kind of a multidimensional disorder, with interactions across neurodevelopment emotional regulation, stress , reward processing , neuroplasticity, inflammatory pathways, sleep, and environmental experience too. Emotional regulation might be one crucial clinical angle, that links everyday psychological experience with changes in affective neural circuitry, so it's not just "mood" in a simple way. Then there's pharmacotherapy, which adds yet another layer of complexity, and honestly it can get confusing fast.

Antidepressant exposure isn't the same for everyone. It varies across individuals due to developmental timing, physiological status , environmental conditions, pharmacological details, and even genetic factors. CYP2C19 and CYP2D6 are especially important, because genetic variation in these enzymes can shape the metabolism of multiple antidepressants , and that's one way it can produce variability in drug exposure [20,60-64]. Still, drug metabolism should not be mistaken for the biological origin of depression itself. Instead, pharmacometabolism can be thought of as only one possible contributor to why treatment responses vary once depression is already present and developing.

So the future of adolescent precision psychiatry probably won't hinge on a single biomarker alone. Rather, a broader scheme should blend together psychological phenotype plus developmental neurobiology, and also clinical psychiatry, pharmacodynamics, pharmacokinetics, pharmacogenetics, and the environmental context around the adolescent. Within this kind of cross disciplinary scaffold, emotional regulation could function as a clinically meaningful psychological phenotype, while CYP2C19 and CYP2D6 might offer pharmacokinetic hints for selected antidepressants. But we still need larger prospective studies, using diverse adolescent populations, before pharmacogenetic information can be integrated confidently into routine care for adolescent depression management.

LIST OF ABBREVIATIONS

BDNF — Brain-derived neurotrophic factor
CPIC — Clinical Pharmacogenetics Implementation Consortium
CYP — Cytochrome P450
CYP2C19 — Cytochrome P450 family 2 subfamily C member 19
CYP2D6 — Cytochrome P450 family 2 subfamily D member 6
HPA — Hypothalamic-pituitary-adrenal
MDD — Major depressive disorder
PD — Pharmacodynamics
PGx — Pharmacogenetics/pharmacogenomics
PK — Pharmacokinetics
SSRI — Selective serotonin reuptake inhibitor

DECLARATIONS

Ethical Consent

For the present study, informed consent from the parents of the participants had been taken and every ethical standard had been taken into consideration for its conduction.

Consent for Publication

The Author gives the full consent to publish the respective manuscript.

Data Availability

No empirical dataset is associated with this illustrative manuscript. The numerical frequencies and quotations are simulated solely for methodological demonstration.

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

Corresponding Author had drafted the manuscript and done overall analysis & the Co- Author had supervised and analysed the manuscript.

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