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MORE ATTENTION TO QUALITY OF PHARMACOTHERAPY IN PSYCHIATRY

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Pharmacotherapy is the most widely used treatment modality for mental disorders. Psychotropics are cheap and scalable treatments and prescribed widely also by doctors other than psychiatrists. Overall, in 2022 a total of 606 875 Finns received at least one prescription for antidepressants, and 256 656 of an antipsychotic drug (1). Pharmacoepidemiology of psychotropic drugs is in Finland not markedly different from the other Nordic countries or OECD countries overall (2,3). Antidepressant use in Finland is close to Nordic average, but use of antipsychotic drugs higher and anxiolytics somewhat high in Nordic comparison (2).

However, despite vast public health importance, pharmacotherapy of mental disorders receives little attention within the medical profession. Existence of effective and scalable treatments that cost only a few euros per month is rarely positively noted. On the contrary, in popular media the default narrative of psychotropic drugs is deeply rooted as negative, with the exceptions of idealized narratives of stimulants for ADHD as life-changing and occasional hype of psychedelics. Use of pharmacotherapy is commonly depicted as an indication of societal problems, or perhaps as the problem itself. It is also elucidating that, for example, the 70 pages of National Mental Health Strategy and Programme for Suicide Prevention 2020–2030 do not include a single word of pharmacotherapy for mental disorders, the most widely available treatment modality in real life (4). Pharmacotherapy is not popular, and as a topic best avoided. A more worrisome observation is that only few psychiatrists appear to perceive knowledge and skill related to the over one hundred psychotropic drugs as valued professional expertise. Our patients may pay a price.

WHAT IS PERCEIVED TO BE WRONG WITH PHARMACOTHERAPY?

It is interesting that from a point of view of evidenced-based medicine, efficacy of pharmacotherapy is actually better documented (in hundreds of double-blind, placebo-controlled randomized trials) than that of other treatment modalities in psychiatry (5). Psychotherapy studies can never be fully blinded, and no universally accepted psychotherapy placebo exists, nor is there any administrational body guarding against publication bias before entrance to market; number of sham-controlled studies of neuromodulation is still limited compared with trials of pharmacotherapy. Influence of pharmacological industry interests potentially biasing findings exists (6), but researcher allegiance is also a well-known problem in psychotherapy studies (7). Efficacy of pharmacotherapies and psychotherapies used in common mental disorders is overall equal (5). Given moderate effectiveness of common psychiatric treatments at best, consistent finding of combining pharmacological and psychosocial treatment modalities to be more effective than either modality alone is important (5). In terms of effect sizes, the efficacy of medications used in psychiatry is broadly comparable to those used in general medicine (8). So, what is the problem?

Aetiology of adult mental disorders is complex, multifactorial and heterogeneous, comprising domains of genetic vulnerability, childhood adversity, neurodevelopmental disorders, temperamental vulnerabilities as well as adulthood psychosocial stressors, among others. Dissecting pathogenetic mechanisms of mental disorders necessitates integrating multiple levels of scientific study and explanation, from molecular to brain circuits and developmental to social factors (9). However, the neurobiological underpinnings of

mental disorders are understood only in part, and no widely applicable biomarkers are available for clinical psychiatrists (10). So, the underlying rationale for biological treatments may appear alien or to lack credibility also by professionals.

Many treatments for mental disorders are at least moderately clinically effective, but there is no "causal" or "curative" treatment. However, optimal treatment is commonly understood by both lay people as well as many mental health professionals – often trained exclusively from a psychosocial perspective - to be more or less entirely psychosocial. Mental disorders are perceived to be (exclusively) derivatives of current and childhood adversities as well as societal problems, and psychotherapy to be the only true treatment of value. Furthermore, nobody can have any conscious observation of abnormal brain function, but we all observe our own internal experiences and observe other peoples' behaviour. Psychosocial treatments appear to correspond to this natural level of experience and are perceived as more compassionate approaches than prescribing drugs. Even a patient fully remitting with aid of pharmacotherapy may well feel "not having received treatment", if the psychosocial component of treatment was thinner than expected. Health benefits and patient satisfaction can be separate and mutually independent phenomena.

CAN PHARMACOTHERAPIES BE SEEN AS PROPER TREATMENTS?

It would be helpful if the rationale for pharmacotherapies would be more widely discussed in medical education. Basic pharmacology is important for doctors in multiple ways, but the higher-level neural effects of psychopharmacological treatments have received little attention (11). They have become foci of scientific study only during this millennium. Unlike basic pharmacological studies focusing on receptors or neuroplasticity effects investigated almost exclusively in animal models, higher-order functions are investigated in human studies of healthy volunteers and real patients, using methodologies of brain imaging and neurocognition. Antidepressants are now known to normalize the negative emotional bias present in most patients with depression (12), and antipsychotics target the dopaminergic salience systems likely aberrant in psychoses (13). Benzodiazepines and antidepressants reduce excessive limbic reactivity present in anxiety disorders. Systems-level neural effects have their counterparts in neurocognition and are observable in neurocognitive testing even before alleviation of symptoms (12), and at least partial normalization of function can be observed. Whether or not, or the degree to which such effects can be seen as "curative" as those of other treatments is a matter of philosophical debate and involves also value judgements. Precisely how psychotherapies exert their effects remains similarly uncertain (14), but valuable attempts to integrate psychological and neurobiological aspects of depression have been made (15). Seen from a broad neurobiological perspective, while psychotherapies may improve emotional regulation in depressive or anxiety disorders by enhancing top-down control, antidepressants may have bottom-up effects by reducing limbic overreactivity (16). Obviously, these effects can be expected to be synergistic.

QUALITY MONITORING OF PHARMACOTHERAPY IS NEEDED

In theory, indications for pharmacological treatments should be based on comprehensive diagnostic evaluation, integrated into an individualized treatment plan, pharmacological options negotiated with patients acknowledging their preferences of avoidable side effects; evolving response and emerging harmful effects carefully monitored, and response critically evaluated. In case of poor response or intolerable side effects the dose should be optimized, or agent should be discontinued, and another agent tried. Outside textbooks and guidelines such procedures can be quite variable, and quality of psychopharmacological treatment is a public health concern.

In the usual clinical psychiatric and primary care practice, there can be problems in all aspects described above (17-19). Particularly outside psychiatric settings, indications for therapy can be vague, monitoring of response or harms minimal, and treatment planning absent. This may lead to unnecessary use of psychotropic drugs for mild symptoms, or choice of a drug with no evidence for efficacy for the specific indication, if any. Furthermore, as a significant proportion of patients is known not to respond to a single drug trial, all treatment responses should be critically evaluated in order to discontinue treatments not effective. Similarly, the time frame of planned treatment should be explicit in medical records, and provided that patient's clinical condition allows, continuation and maintenance treatments should be gradually tapered down as planned. In the absence of response monitoring and use of symptom scales as the necessary tools, patients may be exposed for extended periods

to pharmacotherapy that clearly is not effective but causes significant harms (20).

At present primary care doctors may be requested to renew prescriptions of psychotropics without information on the indication or planned duration of the treatment. At worst, treatments may be ongoing for years without appropriate monitoring and treatment planning. If psychotropic treatments are well monitored, then only treatments with more benefits than harms for the individual are continued and others rapidly terminated. However, poor follow-up and monitoring can turn the balance of benefits and harms upside down.

HOW HELPFUL ARE THERAPEUTIC MONITORING AND PHARMACOGENETIC TESTING IN IMPROVING QUALITY OF CARE?

Psychotropic drugs have side effects, which are highly individual and commonly mild and transient, but can sometimes be severe, harmful and persistent. In particular, weight gain and associated metabolic harms can add to cardiovascular risks and attention is needed already when planning treatment (21). While most of the common and mild adverse effects are relatively predictable based on a drug's pharmacological profile, some rare and serious adverse effects are largely unpredictable. Given widespread use of psychotropic drugs, their adverse effects comprise a public health concern.

Measuring blood levels of a drug, as a part of therapeutic drug monitoring (TDM), may offer an opportunity to improve safety of pharmacotherapy by allowing recognition of abnormally high concentrations causing harms, or abnormally low as a likely cause of non-response (22). While applying TDM routinely to all pharmacological treatments is likely not meaningful and may waste scarce resources (23), targeted TDM in cases of no response or unusual harms is likely well founded. Price of pharmacogenetic testing has markedly declined during the recent years. Selective use of pharmacogenetic testing in cases of abnormal drug-induced harms or refractoriness to usual treatments is another important measure in order to improve quality of pharmacotherapy (24). Psychiatry would benefit from closer collaboration with clinical pharmacology.

CONCLUSIONS

Pharmacotherapies are widely prescribed for mental disorders, but more attention should be devoted to provision of high-quality care. Following principles of measurement-based care is likely to improve patients' outcomes (25). Adherence to treatment guidelines in critical evaluation of indications as well as treatment responses, discontinuing ineffective treatments and switching and combining or augmenting pharmacotherapies could significantly benefit our patients. Concurrent systematic monitoring of drug-induced harms, recognition of pharmacogenetic vulnerabilities and dangerous pharmacological interactions is important for maximizing safety of treatment. Finally, improving quality of pharmacotherapy does not mean that the main focus of treatment should be just providing pharmacotherapy and nothing else. High-quality treatment in psychiatry combines treatment modalities as needed, and it is naturally important to improve availability of evidence-based psychosocial treatments. However, many patients receive pharmacotherapy as their only evidence-based treatment, and that should be safe and effective.

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References:

1. Suomen Lääketilasto 2022. Fimea & Kansaneläkelaitos.

2. Nordic Health & Welfare Statistics https://nhwstat.org/

3. OECD Health Statistics 2023 https://www.oecd.org/health/health-data.htm

4. Kansallinen mielenterveysstrategia ja itsemurhien ehkäisyohjelma vuosille 2020–2030. Sosiaali- ja Terveysministeriön julkaisuja 2020:6.

5. Leichsenring F, Steinert C, Rabung S, Ioannidis JPA. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of recent meta-analyses. World Psychiatry 2022;21:133-145.

6. Waqas A, Baig AA, Khalid MA, Aedma KK, Naveed S. Conflicts of interest and outcomes of clinical trials of antidepressants: An 18-year retrospective study. J Psychiatric Research 2019;116:83-87.

7. Zimmerman JA, Marcus DK. Does Researcher Allegiance Bias Outcomes in Psychotherapy Research? A Quasi-Experimental Secondary Analysis. Clin Psychol Psychother 2024;31(2):e2974. doi: 10.1002/cpp.2974.

8. Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry 2012;200:97-106.

9. Stein DJ, Nielsen K, Hartford A, Gagné-Julien AM, Glackin S, Friston K, Maj M, Zachar P, Aftab A. Philosophy of psychiatry: theoretical advances and clinical implications. World Psychiatry 2024;23:215-232.

10. Abi-Dargham A, Moeller SJ, Ali F, DeLorenzo C, Domschke K, Horga G, Jutla A, Kotov R, Paulus MP, Rubio JM, Sanacora G, Veenstra-VanderWeele J, Krystal JH. Candidate biomarkers in psychiatric disorders: state of the field. World Psychiatry 2023;22:236-262.

11. Aftab A, Stein DJ. Psychopharmacology and explanatory pluralism. JAMA Psychiatry 2022;79:522-523.

12. Godlewska BR, Harmer CJ. Cognitive neuropsychological theory of antidepressant action: a modern-day approach to depression and its treatment. Psychopharmacology (Berl) 2021;238(5):1265-1278.

13. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia - an overview. JAMA Psychiatry 2020;77:201-210.

14. Cuijpers P, Reijnders M, Huibers MJH. The role of common factors in psychotherapy outcomes. Annu Rev Clin Psychol 2019;15:207-31.

15. Disner SG, Beevers CG, Haigh EAP, Beck AT. Neural mechanisms of the cognitive model of depression. Nat Rev Neurosci 2011;12:467-77.

16. DeRubeis RJ, Siegle GJ, Hollon SD. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. Nat Rev Neurosci 2008;9:788-96.

17. Vuorilehto MS, Melartin TK, Riihimäki K, Isometsä ET. Pharmacological and psychosocial treatment of depression in primary care: Low intensity and poor adherence and continuity. J Affect Disord 2016;202:145-52.

18. Lähteenvuo M, Taipale H, Tanskanen A, Rannanpää S, Tiihonen J. Courses of treatment and risk factors for treatment-resistant depression in Finnish primary and special healthcare: A nationwide cohort study. J Affect Disord 2022;308:236-242.

19. von Knorring J, Baryshnikov I, Jylhä P, Talaslahti T, Heikkinen M, Isometsä E. Prospective study of antidepressant treatment of psychiatric patients with depressive disorders: treatment adequacy and outcomes. BMC Psychiatry 2023;23:888. doi: 10.1186/s12888-023-05390-8.

20. Isometsä E. Milloin masennuslääke on turha? Yleislääkäri 2023;4:13-15.

21. McIntyre RS, Kwan ATH, Rosenblat JD, Teopiz KM, Mansur RB. Psychotropic Drug-Related Weight Gain and Its Treatment. Am J Psychiatry 2024; 181:26-38.

22. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, Eckermann G, Egberts K, Gerlach M, Greiner C, Gründer G, Haen E, Havemann-Reinecke U, Hefner G, Helmer R, Janssen G, Jaquenoud E, Laux G, Messer T, Mössner R, Müller MJ, Paulzen M, Pfuhlmann B, Riederer P, Saria A, Schoppek B, Schoretsanitis G, Schwarz M, Gracia MS, Stegmann B, Steimer W, Stingl JC, Uhr M, Ulrich S, Unterecker S, Waschgler R, Zernig G, Zurek G, Baumann P. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry 2018;51:9-62.

23. Grunze H. Measuring serum concentrations of psychotropics- Valuable tool for decision making or waste of money? Eur Neuropsychopharmacol 2023;76:20-22.

24. Arnone D, Omar O, Arora T ym. Effectiveness of pharmacogenomic tests including CYP2D6 and CYP2C19 genomic variants for guiding the treatment of depressive disorders: Systematic review and meta-analysis of randomised controlled trials. Neurosci Biobehav Rev 2023;144:104965.

25. Xiao L, Qi H, Zheng W, Xiang YT, Carmody TJ, Mayes TL, Trivedi MH, Wang G. The effectiveness of enhanced evidence-based care for depressive disorders: a meta-analysis of randomized controlled trials. Transl Psychiatry 2021;11(1):531. doi: 10.1038/s41398-021-01638-7.