PHARMACIA

Pharmacia 71: 1–6
DOI 10.3897/pharmacia.71.e125942

Research Article

A new approach for objective monitoring of the pharmacological-treatment response in recurrent depressions

Rumen Dimitrov[1], Evelina Haralanova[1], Ivan Milanov[1], Sava Ognyanov[2], Iva Parvova[3], Emil Milushev[1]

1 *University Hospital of Neurology and Psychiatry "St. Naum", Medical University of Sofia, 1 Louben Rousev str., Sofia 1113, Bulgaria*
2 *Laboratory of Social Pharmacy, Faculty of Chemistry and Pharmacy, Sofia University "Saint Kliment Ohridski", 1, James Bourchier blvd., Sofia 1164, Bulgaria*
3 *Department of Rheumatology, Medical University of Sofia, 13, Urvich str., Sofia 1612, Bulgaria*
Corresponding author: Sava Ognyanov (s.ognianov@gmail.com)

Received 22 April 2024 ♦ **Accepted** 8 May 2024 ♦ **Published** 20 June 2024

Citation: Dimitrov R, Haralanova E, Milanov I, Ognianov S, Parvova I, Milushev E (2024) A new approach for objective monitoring of the pharmacological-treatment response in recurrent depressions. Pharmacia 71: 1–6. https://doi.org/10.3897/pharmacia.71.e125942

Abstract

Depressive disorders are among the most important psychiatric problems. In everyday clinical practice, their symptoms and, respectively, their response to pharmacological treatment are both evaluated and measured subjectively. In the present paper, we apply a new approach for objective monitoring of the pharmacological-treatment response in patients with recurrent depressions. The applied method is user-friendly, easy-to-perform, and not time-consuming (1 test = 1 min), thus allowing repeatable examinations of many patients. The results show that the pre-treatment examination could discriminate between patients and healthy controls by revealing objectively measurable psychomotor retardation (in terms of locomotor hypo-activity and brady-reactivity) in the depressive group. After effective psychopharmacological treatment in a psychiatric clinic, the revealed psychomotor retardation is significantly improved (although not fully normalized) during the post-treatment examination at the time of discharge. The conclusion is that the new approach is reliable and sensitive enough to serve as a surrogate pharmacodynamic biomarker in patients with recurrent depressions.

Keywords

depression, pharmacological treatment, pharmacodynamic biomarkers, locomotor behavior, psychomotor retardation

Introduction

Depression is a psychiatric illness that currently affects more than 300 million people, or about 4.4 percent of the world's population (Hasin et al. 2018). It is the most disabling disease, covering 7.5% of the average life expectancy of a person (Friedrich 2017). Psychomotor disturbances (PMD) are cardinal features of endogenous (melancholic) depressions with important diagnostic, pathophysiological, and therapeutic implications (Schrijvers et al. 2008). They are the only objectively measurable dimension of depressive psychopathology (Faurholt-Jepsen et al. 2015; Terziivanova et al. 2018) and could be informative on underlying neurobiological mechanisms (Wüthrich et al. 2023).

According to the current diagnostic criteria of the main international classifications (ICD-10 and DSM-5), recurrent depressions involve PMD with two opposite deviations from the norm (retardation or agitation). However, mostly psychomotor retardation (slowness of movement) is explicitly discussed in the scientific literature as a defining feature of these depressions (Widlöcher 1983; Sachdev et al. 1994). Therefore, not surprisingly, this direction of psy-

chomotor deviation has attracted the attention of almost all researchers in the field (Beheydt et al. 2015). Unlike psychomotor agitation, which is a shared characteristic with endogenous manic states, psychomotor retardation (PMR) is closely related to the neurobiological mechanisms of melancholic depressions (Calugi et al. 2011) and to their improvement by pharmacological treatment (Bennabi et al. 2013). There is a positive correlation between the severity of depression and PMR: the more severe depression, the more pronounced PMR (Romanowicz et al. 2019).

The motor component (motor activity or motor behavior) of the PMR in depressive patients is particularly suitable for objective assessment (Todder et al. 2009; Burton et al. 2013; Lohr et al. 2013). As a rule, it also correlates with the severity of depression (Raoux et al. 1994; Razavi et al. 2011). More specifically, gait speed (locomotor activity or locomotor behavior) is a relatively well-studied objective component of the depressive PMR (Sloman et al. 1982; Lemke et al. 2000; Haralanov et al. 2021). Most researchers have used actigraphy and other objective methods for more reliable recording and measuring of gait (locomotor) patterns in depressive patients (Belvederi Murri et al. 2020). Up to now, the available objective and quantitative instrumental methods for gait (locomotion) analysis in depressive patients have been restricted to research purposes, mainly because these methods in principle are rather sophisticated, expensive, and time-consuming, thus being inconvenient for regular clinical use. In their routine practice, clinicians continue to evaluate and measure depressive PMR subjectively through observation and observer-rated scales (Dantchev et al. 1998). However, such subjective approaches make it difficult to generate precise and reliable measurements (Iverson 2004). Therefore, a new, less sophisticated, inexpensive, and user-friendly instrumental method for a more precise and reliable objective quantification of locomotor behavior (LMB) as an objective marker of PMR in depressive patients is needed so as to be applied in everyday clinical practice not only for evaluating the severity of the actual depressive state but also for a subsequent objective monitoring of the pharmacological-treatment response.

Consistent with this hitherto unmet need, the aims of the present study were: 1) To test in everyday clinical practice an original method for objective evaluation of movement patterns by investigating the psychomotor retardation in patients with recurrent depressions; 2) To compare the investigated patients with well-matched healthy control persons; 3) To follow up both groups by a second investigation after a period of about one month; and 4) To determine whether the tested method could be used as a new approach for objective monitoring of the pharmacological-treatment response in patients with recurrent depressive states.

Material and methods

For the purpose of the study, 60 depressive patients (DP) aged between 19 and 59 years have been examined. They were admitted to inpatient treatment at the First Psychiatric Clinic of the "St. Naum" University Hospital of Neurology and Psychiatry in relation to a major depressive episode within Recurrent Depressive Disorder (RDD) with codes F33.1 and F33.2, according to the diagnostic criteria of ICD-10. The severity of the depressive state met the criteria for a moderate depressive episode. From them, 32 DP were selected, for which it was possible to carry out a double examination (before and after pharmacological treatment). The specific treatment regimen for each individual depressed patient was at the discretion of the respective treating physicians. The main criteria for their inclusion in the re-examination were: 1) there was a clinically detectable improvement in their depressive state; 2) to give written consent not only for the first but also for the repeated examination. In addition, 72 healthy controls (HC) aged between 20 and 58 years were examined. From them, 44 HCs (matched by age, sex, height, weight, and education with DP) were selected, for whom it was possible to carry out a re-examination.

All subjects signed an "Informed Consent for Participation" after familiarizing themselves with the research methodology. The study was approved by the Ethics Committee of the University Hospital of Neurology and Psychiatry "St. Naum" in Sofia, Bulgaria. The study design was longitudinal, involving examining each of the groups twice and subsequent intragroup and intergroup comparisons of the obtained data. The initial examination for DP was conducted immediately before the start of hospital treatment (baseline = pre-treatment assessment) and the second on the day before discharge (follow-up = post-treatment assessment). HC were re-examined (follow-up assessment) at an interval of 3–4 weeks after their first examination (baseline assessment) to match the intervals at which DP were examined. We used an original method for integrative objective recording, representing, and measuring LMB at the single-patient level (Haralanov et al. 2021). It is based on the classical equilibriometric method "cranio-corpography" (CCG), invented by Claus-Frenz Claussen, one of the founders of clinical equilibriometry (Claussen, 2000). We applied the computerized ultrasonic version of CCG (Comp-US-CCG), produced by the German company, which allows a very precise spatial-temporal equilibriometric quantification of the head and body movements during the execution of the classical locomotor "stepping-test" of Unterberger (Haralanov et al. 2002; Haralanov et al. 2021). The test consists of stepping in place with eyes closed for 1 min, starting from the standard standing position of Romberg (Fig. 1).

The stepping-test Comp-US-CCG is easy-to-perform, user-friendly, reliable, reproducible, noninvasive, and not time-consuming (1 test = 1 min). Moreover, its results are understandable for clinicians, and the method could be routinely applied in clinical practice by the treating psychiatrists themselves or by their technical assistants, e.g., nurses or students. Quantitative evaluation is achieved by a well-established polar reference net (Claussen 2000). Movements of the head and shoulder markers then appear

Figure 1. Stepping-test computerized ultrasonic cranio-corpo-graphy.

as radar-like images of four moving objects, progressing in an interrelated direction. The computer program automatically measures some standard CCG parameters, thus quantifying the individual LMB, which could serve as an objective measure of PMD at the single-patient level. Previously, it was discovered that optimal equilibriometric quantification of PMR in depressive patients might be achieved by two essential CCG parameters: „lateral sway“ and „number of steps per minute “(Terziivanova et al. 2018; Haralanov et al. 2021). Their numerical values are displayed on the computer screen, along with a visual comparison with the limits of normative data. Thus, immediately after the end of each test, it can be seen whether the value of a given CCG parameter is outside or inside the normal limits. Together with the numerical data, the graphical gestalt CCG images might also serve to discriminate between normal and abnormal LMB, even at first glance. The CCG parameter „lateral sway“ measures (in centimeters) the maximal range of alternating (inverted-pendulum-like) medial-lateral and lateral-medial head and body movements during each swing phase of the locomotor cycle. This unstable one-leg position (see Fig. 1) leads initially to a medial-lateral displacement of the head and shoulders (contralateral to the lifted leg), followed by a reflexive (defensive) movement in the opposite direction that is aimed at preventing an eventual fall. Although such fluctuations of the upper part of the body are measured in space, they indirectly indicate the velocity (which is in fact a temporal measure) of unconscious and automatic psychomotor ***reactivity*** that helps to maintain equilibrium during stepping locomotion. So, large lateral sway indicates slower psychomotor reactivity (brady-reactivity). The second essential CCG parameter that is relevant for PMR is the „number of steps per minute.“ It reflects the self-paced rate of conscious and volitional, self-initiated, goal-directed psychomotor ***activity***. A lower number of steps indicates reduced psychomotor activity (hypo-activity). The normal numerical values of these two psychomotor CCG parameters could be conceived as indicating normal LMB in healthy subjects. Their lower and upper limits (provided by the computer program “Winbalance”) have been determined after systematic investigations of hundreds of clinically healthy controls (Claussen 2000). The following analyses/methods were used for the statistical processing of the collected data by SPSS: Descriptive statistics, independent samples T-test; Paired samples T-test; Paired samples GLM; Wilcoxon test.

Results

The main results of the study are illustrated graphically in Figs 2, 3.

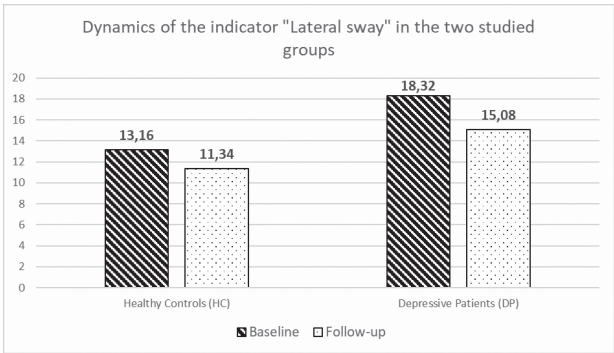

Figure 2. Dynamics of the indicator “Lateral sway” in the two studied groups.

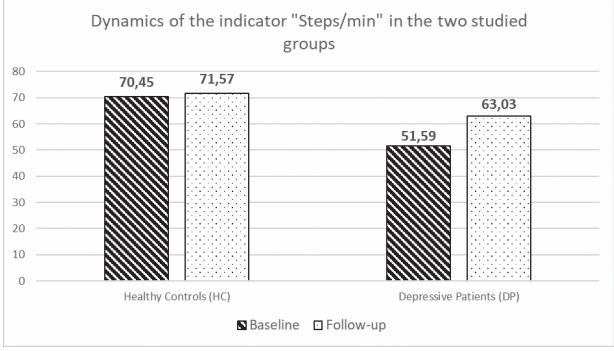

Figure 3. Dynamics of the indicator “Steps/min” in the two studied groups.

Descriptive statistics of Comp-US-CCD results for DP are presented in Table 1 and for HC in Table 2.

A t-test for two independent samples in the initial study (pre-treatment comparisons) revealed statistically significant differences between DP and HC, measured by the CCG parameter “lateral sway” ($t(73) = 6.189$; $p < 0.001$). It has a higher value in DP ($M = 18.32$; $SD = 6.645$) compared to HC ($M = 13.16$; $SD = 2.879$), which indicates the presence of psychomotor brady-reactivity in patients with recurrent depressions. Statistically significant differences were also found between DP and HC, measured by the CCG parameter “number of steps per minute” ($t(73) = -5.494$; $p < 0.001$). It has a lower value in DP ($M = 51.59$; $SD = 16.176$) compared to HC ($M = 70.45$; $SD = 13.308$),

Table 1. Descriptive statistics of the depressive patients.

Baseline (pre-treatment)	Lateral sway	Number of steps per minute
N = 32	M = 18.32 (SD = 6.635)	M = 51.59 (SD = 16.176)
Follow-up (post-treatment)		
N = 32	M=15.08 (SD = 4.537)	M = 63.03 (SD = 15.111)

Note: N = number of investigated subjects; M = mean value; SD = standard deviation.

Table 2. Descriptive statistics of the healthy controls.

Baseline	Lateral sway	Number of steps per minute
N = 44	M = 13.16 (SD = 2.879)	M = 70.45 (SD = 13.308)
Follow-up		
N = 44	M = 11.34 (SD = 3.275)	M = 71.57 (SD = 12.161)

Note: N = number of investigated subjects; M = mean value; SD = standard deviation.

which indicates the presence of psychomotor hypo-activity in them. In general, this finding can be interpreted as an objectively measurable PMR in the investigated patients with recurrent depressions.

The analysis of psychomotor differences after the pharmacological treatment (pre-treatment/post-treatment comparisons) in DP based on the t-test for dependent samples, as well as on the basis of the test of Wilcoxon for dependent samples, showed statistically significant differences in the CCG parameter „lateral sway" ($t(31) = 4.38$; $p<0.001$), as well as the CCG parameter „number of steps per minute" ($t(31) = 4.497$; $p < 0.001$). After the pharmacological treatment, lower lateral sway values (M = 15.08; SD = 4.537) were found in DP compared to the pre-treatment values (M = 18.32; SD = 6.635), which indicates an objectively measurable therapeutic influence of the existing psychomotor brady-reactivity in them. Regarding the number of steps per minute, higher post-treatment values (M = 63.03; SD = 15.111) were found compared to the values before pharmacological treatment (M = 51.59; SD = 16.176), which indicates an objectively measurable therapeutic effect of the existing psychomotor hypo-activity in them. In general, this finding can be interpreted as an objectively measurable reduction of the PMR existing before the pharmacological treatment in the investigated patients with recurrent depressions.

No statistically significant differences were found in the psychomotor functions of the HC (baseline/follow-up comparisons) in the lateral sway ($t = 0.951$, $p = 0.347$) between the baseline (M = 13.16; SD = 2.879) and the follow-up examination (M = 11.34; SD = 3.275), as well as in the number of steps per minute ($t = 0.841$, $p = 0.405$) between the baseline (M = 70.45; SD = 13.308) and the follow-up examination (M = 71.57; SD = 12.161). This shows that, unlike in DP, in HC there are no significant objectively measurable dynamics between the two examinations, which confirms the replicability and reliability of the methodology used.

Post-treatment and follow-up comparisons also found statistically significant differences between DP and HC regarding the lateral sway ($t(73) = 4.143$; $p < 0.001$) as well as the number of steps per minute ($t(73) = -2.676$; $p < 0.01$), irrespective of the significant post-treatment reduction of the pre-existing PMR in DP. After the pharmacological treatment, higher values of the lateral sway were found in DP (M = 15.08; SD = 4.537) compared to the values of the follow-up examination in HC (M = 11.34; SD = 3.275). Such a finding indicates that, although significantly improved by successful pharmacological treatment, the pre-existing psychomotor brady-reactivity in DP is not yet fully normalized and continues to differ from the norm to an objectively measurable degree. The situation is similar with regard to the number of steps per minute, where after pharmacological treatment in DP, lower values are found (M = 63.03; SD = 15.111), compared to the values of the HC (M = 71, 57; SD = 12.161). Such a finding indicates that, despite the statistically significant improvement of the pre-existing psychomotor hypoactivity, the latter has not yet been completely normalized after the pharmacological treatment, and its value continues to differ from the norm in an objectively measurable degree. It can be summarized that after successful pharmacological treatment (approaching normal LMB), the pre-existing PMR is not completely normalized, and both psychomotor brady-reactivity and psychomotor hypo-activity are still present (although significantly reduced), and therefore, their objectively measurable indicators continue to significantly differ from the norm.

Discussion

In general, the main results of the present study confirm our hypothesis that the objective and quantitative method can be used as a new approach for objective monitoring of the pharmacological-treatment response in patients with recurrent depressions. The results of the baseline/pre-treatment intergroup comparisons show that there is a statistically significant difference in the psychomotor functions of the two groups (in terms of stepping-test LMB), measured by Comp-US-CCG.

Psychomotor brady-reactivity and psychomotor hypo-activity have been established as objectively measurable manifestations of PMR. The pre-treatment and post-treatment dynamics in the DP show that the clinically observed therapeutic improvement of the depressive state is accompanied by a corresponding statistically significant improvement of the objectively measurable PMR. The data we obtained are consistent with data from previous studies measuring depressive PMR with other (more sophisticated and time-consuming) methods (Buyukdura et al, 2011). Analogous data regarding PMR have been established by other methods for objective measurement of the depressive gait (locomotion) (e.g., Wendorf et al. 2002; Aybek et al. 2008). They are also consistent with previous studies with the method we used in patients with endogenous (unipolar and bipolar) depressions (Terziivanova et al. 2018; Haralanov et al. 2021). A conclusion could be

drawn that the objective and quantitative measurement of the stepping-test LMB by Comp-US-CCG enables reliable intergroup differentiation between DP, PMR, and HC.

As for the intragroup dynamics between baseline and follow-up LMB in the HC as well as between pre-treatment and post-treatment LMB in the DP, our data show that the two types of dynamics are fundamentally different. While in HC there are no significant dynamics in both measured CCG parameters (lateral sway and number of steps per minute), in DP there are statistically significant dynamics towards improvement of the LMB (also on both measured CCG parameters) after the successful pharmacological treatment. These findings give us reason to assume that both measured components of PMR (psychomotor hypo-activity as well as brady-reactivity) are favorably affected by the pharmacological treatment. It is important to note that despite the objectively measurable and significant improvement of PMR in the DP, their LMB is not fully normalized. This means that, after hospital treatment, the investigated DP has not yet achieved full remission. Such a finding should not surprise us, since it is known from clinical practice that discharge from a psychiatric clinic is not equivalent to full remission.

Statistically significant differences between the LMB before and after clinically effective pharmacological treatment demonstrate the direct relationship between improvement in clinically reported depressive symptoms and corresponding improvement in objectively measured PMR. In this regard, the results of our study are consistent with other objective studies on the improvement of psychomotor and gait (locomotor) functions by pharmacological treatment of the depressive state (Raoux et al. 1994; Paleacu et al. 2007; Todder et al. 2009) that have been carried out over the years. What is new is the use of a unique method for objective registration and precise measurement of LMB as an objective marker for depressive PMR, whose application in everyday clinical practice is completely real, as the duration of the individual examination is only 1 minute. Such an approach allows repeated measurements of LMB over the course of treatment in patients with recurrent depression and the subsequent elicitation of therapeutic trajectories, from which it is evident at a glance whether there is a trend for improvement or deterioration or for a lack of effect of the applied treatment. From this point of view, the present study is a proof of concept, having previously been substantiated at the theoretical level (Haralanov et al. 2021), by demonstrating the feasibility in everyday clinical practice of the application of the stepping-test Comp-US-CCG for objective monitoring of the pharmacological-treatment response in DP. From a theoretical point of view, our data also shed new light on the mechanisms of recurrent depressions, in particular on the relationships between subjective depressive symptoms and objectively measurable PMR, as well as on the mechanisms of their improvement after effective pharmacological treatment. From such a point of view, the method we used can be used in everyday clinical practice not only for dynamic monitoring of the pre-existing PMR but also for supporting the objective diagnostics of recurrent depressions.

Limitations and acceptable assumptions

Along with the indisputable advantages of the approach used in the present study, we should also note some of its limitations. The most important of them is demonstrating the possibility of objectively monitoring the effect of the pharmacological treatment only when PMR was present

before the treatment. As some preliminary studies using the same method have shown (Terziivanova et al. 2018; Haralanov et al. 2021), its use in depressed patients with psychomotor agitation is most effective when manic-like behavioral activation is present. In principle, it is in the opposite direction of deviation from the norm, and its therapeutic improvement is in the direction of approaching the norm (and even normalization) by slowing down the available manic-like psychomotor hyper-activity and/or tachy-reactivity. Another important limitation is the fact that psychiatrists are not used to applying technical (apparatus) methods and devices in their everyday clinical practice and are therefore critical of the possibility of applying them not only for scientific but also for practical purposes. In this case, the methodology and equipment are extremely user-friendly and easy to apply even by non-medical personnel, which is proven by their routine use in the field of clinical equilibriometry (Claussen 2000). On the other hand, with the advancement of technologies (wearable and inertial sensors, smartphones, computational psychiatry, machine learning, artificial intelligence, and the like), the practical application of the methodical approach we used might become increasingly easier, cheaper, more precise, and less time-consuming.

Conclusion

After introducing a fundamentally new methodical approach to objectively assess patients with recurrent depressions, we were able to show that their objectively measurable PMR is significantly reduced (although not completely normalized) after clinically effective pharmacological treatment in hospital settings. Both investigated psychomotor indicators (in terms of locomotor hypo-activity and brady-reactivity) during the pre-treatment depressive state improved statistically significantly during the post-treatment recording. These findings allow us to assume that our methodological approach can be used in the everyday clinical practice of psychiatry as a surrogate pharmacodymanic biomarker of the pharmacological-treatment response in recurrent depressions with PMR. Technological development could further facilitate the application of the method, possibly through a special app on a smartphone.

References

Aybek S, Berney A, Salarian A, et al. (2008) Objective evaluation of gait parameters and psychomotor retardation in major depression. Parkinson Related Disord 14(Suppl 1): S69. https://doi.org/10.1016/S1353-8020(08)70331-6

Beheydt LL, Schrijvers D, Docx L, et al. (2015) Psychomotor retardation in elderly untreated depressed patients. Front Psychiatry 5: 196. https://doi.org/10.3389/fpsyt.2014.00196

Belvederi Murri M, Triolo F, Coni A, et al. (2020) Instrumental assessment of balance and gait in depression: A systematic review. Psychiatry Res 284: 112687. https://doi.org/10.1016/j.psychres.2019.112687

Bennabi D, Vandel P, Papaxanthis C, et al. (2013) Psychomotor retardation in depression: a systematic review of diagnostic, pathophysiologic, and therapeutic implications. BioMed Research International 2013: 158746. https://doi.org/10.1155/2013/158746

Burton C, McKinstry B, Szentagotai Tătar A, et al. (2013) Activity monitoring in patients with depression: a systematic review. Journal of Affective Disorders 145(1): 21–28. https://doi.org/10.1016/j.jad.2012.07.001

Buyukdura JS, McClintock SM, Croarkin PE (2011) Psychomotor retardation in depression: biological underpinnings, measurement, and treatment. Progress in Neuro-Psychopharmacology & Biological Psychiatry 35(2): 395–409. https://doi.org/10.1016/j.pnpbp.2010.10.019

Calugi S, Cassano GB, Litta A, et al. (2011) Does psychomotor retardation define a clinically relevant phenotype of unipolar depression? Journal of Affective Disorders 129(1–3): 296–300. https://doi.org/10.1016/j.jad.2010.08.004

Claussen C-F (2000) Cranio-corpo-graphy: 30 years of equilibriometric measurements of spatial and temporal head, neck and trunk movements. In: Claussen C-F, Haid CT, Hofferberth B (Eds) Equilibrium Research, Clinical Equilibriometry and Modern Treatment. Elsevier, Amsterdam-New York-Oxford-Tokyo, 249–259.

Dantchev N, Widlöcher DJ (1998) The measurement of retardation in depression. The Journal of Clinical Psychiatry 59(Suppl 14): 19–25.

Faurholt-Jepsen M, Brage S, Vinberg M, et al. (2015) Electronic monitoring of psychomotor activity as a supplementary objective measure of depression severity. Nordic Journal of Psychiatry 69(2): 118–125. https://doi.org/10.3109/08039488.2014.936501

Friedrich MJ (2017) Depression is the leading cause of disability around the world. JAMA 317(15): 1517. https://doi.org/10.1001/jama.2017.3826

Haralanov S, Claussen C-F, Haralanova E, et al. (2002) Computerized ultrasonographic cranio-corpo-graphy and abnormal psychomotor activity in psychiatric patients. The International Tinnitus Journal 8(2): 72–76.

Haralanov S, Haralanova E, Bogdanova D, et al. (2021) Integrative objective quantification of individual locomotor behavior in depressive patients: Implications for their stratification and personalized treatment monitoring. In: Gargiulo PA, Mesones Arroyo HL (Eds) Psychiatry and Neuroscience Update: From Epistemology to Clinical Psychiatry. Springer, Nature Switzerland AG, 555–574. https://doi.org/10.1007/978-3-030-61721-9_39

Hasin DS, Sarvet AL, Meyers JL, et al. (2018) Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiatry 75: 336–346. https://doi.org/10.1001/jamapsychiatry.2017.4602

Iverson GL (2004) Objective assessment of psychomotor retardation in primary care patients with depression. Journal of Behavioral Medicine 27(1): 31–37. https://doi.org/10.1023/B:JOBM.0000013642.43978.f9

Lemke MR, Wendorff T, Mieth B, et al. (2000) Spatiotemporal gait patterns during over ground locomotion in major depression compared with healthy controls. Journal of Psychiatric Research 34(4–5): 277–283. https://doi.org/10.1016/S0022-3956(00)00017-0

Lohr JB, May T, Caligiuri MP (2013) Quantitative assessment of motor abnormalities in untreated patients with major depressive disorder. Journal of Affective Disorders 146(1): 84–90. https://doi.org/10.1016/j.jad.2012.08.043

Paleacu D, Shutzman A, Giladi N, et al. (2007) Effects of pharmacological therapy on gait and cognitive function in depressed patients. Clinical Neuropharmacology 30: 63–71. https://doi.org/10.1097/01.wnf.0000240949.41691.95

Raoux N, Benoit O, Dantchev N, et al. (1994) Circadian pattern of motor activity in major depressed patients undergoing antidepressant therapy: relationship between actigraphic measures and clinical course. Psychiatry Research 52(1): 85–98. https://doi.org/10.1016/0165-1781(94)90122-8

Razavi N, Horn H, Koschorke P, et al. (2011) Measuring motor activity in major depression: the association between the Hamilton Depression Rating Scale and actigraphy. Psychiatry Research 190(2–3): 212–216. https://doi.org/10.1016/j.psychres.2011.05.028

Romanowicz KA, Kozłowska K, Wichniak A (2019) Psychomotor retardation in recurrent depression and the related factors. Advances in Psychiatry and Neurology 28(3): 208–219. https://doi.org/10.5114/ppn.2019.89129

Sachdev P, Aniss AM (1994) Slowness of movement in melancholic depression. Biological Psychiatry 35(4): 253–262. https://doi.org/10.1016/0006-3223(94)91256-4

Schrijvers D, Hulstijn W, Sabbe BG (2008) Psychomotor symptoms in depression: a diagnostic, pathophysiological and therapeutic tool. Journal of Affective Disorders 109(1–2): 1–20. https://doi.org/10.1016/j.jad.2007.10.019

Sloman L, Berridge M, Homatidis S, et al. (1982) Gait patterns of depressed patients and normal subjects. The American Journal of Psychiatry 13: 94–97. https://doi.org/10.1176/ajp.139.1.94

Terziivanova P, Haralanova E, Milushev E, et al. (2018) Objective quantification of psychomotor disturbances in patients with a major depressive episode. Journal of Evaluation in Clinical Practice 24(4): 826–831. https://doi.org/10.1111/jep.12916

Todder D, Caliskan S, Baune BT (2009) Longitudinal changes of day-time and night-time gross motor activity in clinical responders and non-responders of major depression. The World Journal of Biological Psychiatry 10(4): 276–284. https://doi.org/10.3109/15622970701403081

Wendorff T, Linnemann M, Lemke MR (2002) Locomotion and depression. Clinical and physiological aspects of gait alterations in Parkinson's disease and major depression. Fortschritte der Neurologie-Psychiatrie 70(6): 289–296. https://doi.org/10.1055/s-2002-32025

Widlöcher DJ (1983) Psychomotor retardation: clinical, theoretical, and psychometric aspects. Psychiatr. Medical Clinics of North America 6: 27–40. https://doi.org/10.1016/S0193-953X(18)30838-4

Wüthrich F, Lefebvre S, Mittal VA, et al. (2023) The neural signature of psychomotor disturbance in depression. Molecular Psychiatry 29: 317–326. https://doi.org/10.1038/s41380-023-02327-1