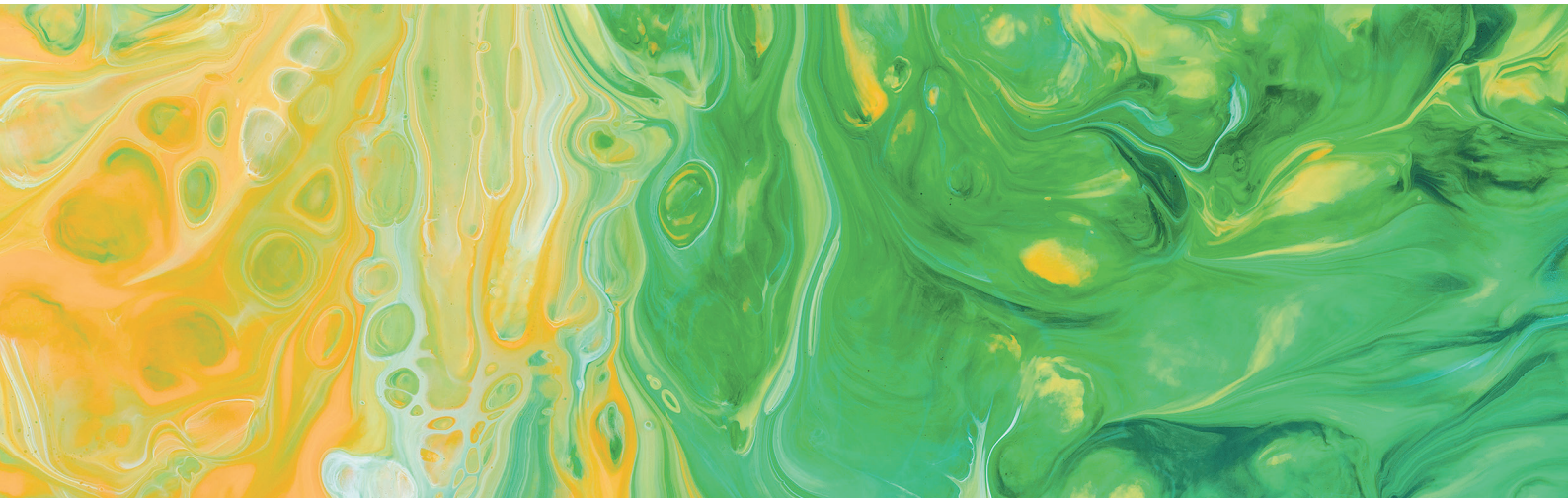
Consortium PSYCHIATRICUM

2023 | Volume 4 | Issue 1 | www.consortium-psy.com | ISSN 2712–7672 (Print) | ISSN 2713-2919 (Online)

Dysregulation of Long Intergenic Non-Coding RNA Expression in the Schizophrenia Brain Page 5



Consortium
PSYCHIATRICUM

Consortium Psychiatricum
Peer-reviewed quarterly medical journal

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By decision of Scopus Content Selection & Advisory Board (CSAB), on 06.12.2022 the scientific journal Consortium Psychiatricum was accepted for indexing in the Scopus database. The corresponding entry can be found in the Scopus Title list published in February 2023 at Elsevier.com.

Based on the letter by the Higher Attestation Commission under the Ministry of Science and Higher Education of the Russian Federation from 06.12.2022 № 02-1198, journals, included in the international database Scopus, are equivalent to the K1 category publications of the Commission's List.

Scopus Title list

Volume 4 Issue 1
ISSN 2712-7672 (Print)
ISSN 2713-2919 (Online)
Frequency: 4 times a year. Signed for printing: 28.03.2023
Printing House: Mediacolor LLC, 19, Signalny proesd, Moscow, Russia, 127273

Consortium
PSYCHIATRICUM

Consortium Psychiatricum
Научный медицинский журнал

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На основании Письма ВАК Минобрнауки России от 06.12.2022 № 02-1198 журналы, входящие в международную базу данных Scopus, приравниваются к изданиям категории К1 Перечня ВАК.

Список журналов, индексируемых в Scopus

Том 4 Выпуск 1
ISSN 2712-7672 (Print)
ISSN 2713-2919 (Online)
Журнал зарегистрирован Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций
Свидетельство о регистрации ПИ № ФС 77-78122 от 13 марта 2020 г. Периодичность: 4 раза в год. Дата выхода в свет: 28.03.2023.
Типография: ООО “Медиаколор“, 127273, г. Москва, Сигнальный проезд, д. 19 . Тираж: 320 экз. Распространяется бесплатно

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Dysregulation of Long Intergenic Non-Coding RNA Expression in the Schizophrenia Brain

Изменения экспрессии длинных некодирующих РНК при шизофрении

doi: 10.17816/CP219

Original research

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ABSTRACT

BACKGROUND: Transcriptomic studies of the brains of schizophrenia (SZ) patients have produced abundant but largely inconsistent findings about the disorder's pathophysiology. These inconsistencies might stem not only from the heterogeneous nature of the disorder, but also from the unbalanced focus on particular cortical regions and protein-coding genes. Compared to protein-coding transcripts, long intergenic non-coding RNA (lincRNA) display substantially greater brain region and disease response specificity, positioning them as prospective indicators of SZ-associated alterations. Further, a growing understanding of the systemic character of the disorder calls for a more systematic screening involving multiple diverse brain regions.

AIM: We aimed to identify and interpret alterations of the lincRNA expression profiles in SZ by examining the transcriptomes of 35 brain regions.

METHODS: We measured the transcriptome of 35 brain regions dissected from eight adult brain specimens, four SZ patients, and four healthy controls, using high-throughput RNA sequencing. Analysis of these data yielded 861 annotated human lincRNAs passing the detection threshold.

RESULTS: Of the 861 detected lincRNA, 135 showed significant region-dependent expression alterations in SZ (two-way ANOVA, BH-adjusted p <0.05) and 37 additionally showed significant differential expression between HC and SZ individuals in at least one region (*post hoc* Tukey test, p <0.05). For these 37 differentially expressed lincRNAs (DELs), 88% of the differences occurred in a cluster of brain regions containing axon-rich brain regions and cerebellum.

Functional annotation of the DEL targets further revealed stark enrichment in neurons and synaptic transmission terms and pathways.

CONCLUSION: Our study highlights the utility of a systematic brain transcriptome analysis relying on the expression profiles measured across multiple brain regions and singles out white matter regions as a prospective target for further SZ research.

АННОТАЦИЯ

ВВЕДЕНИЕ: Исследования транскриптома мозга пациентов с диагнозом шизофрении (ШЗ) не дали однозначной картины механизмов, лежащих в основе этого расстройства. Данная проблема связана не только с возможной гетерогенностью ШЗ, но также с несбалансированным фокусом исследований на определенных областях коры полушарий и экспрессии белок-кодирующих генов. По сравнению с белок-кодирующими генами, длинные некодирующие РНК (дкРНК) демонстрируют значительно большую специфичность и динамику паттернов экспрессии, что позиционирует их как перспективные маркеры молекулярных изменений мозга при ШЗ. Кроме того, растущее понимание системного характера ШЗ требует более систематического анализа экспрессии дкРНК, охватывающего множественные регионы мозга.

ЦЕЛЬ: Идентифицировать и интерпретировать изменения профилей экспрессии дкРНК при ШЗ в 35 регионах мозга.

МЕТОДЫ: Мы провели анализ транскриптома 35 областей мозга четырех пациентов с диагнозом ШЗ и четырех человек из группы контроля, используя высокопроизводительное секвенирование РНК.

РЕЗУЛЬТАТЫ: Из 861 детектированной дкРНК 135 продемонстрировали глобально значимые изменения уровней экспрессии при ШЗ (двусторонний дисперсионный анализ, скорректировано методом Бенджамини–Хохберга p <0,05). Из них 37 дкРНК показали значимые изменения, локализованные в одном или нескольких регионах мозга (тест Тьюки, p <0,05). Из этих изменений 88% произошли в регионах белого вещества мозга и мозжечке. Функциональная аннотация 37 дкРНК выявила значимую корреляцию с генами нейронов и генами, кодирующими элементы синаптической передачи сигнала.

ЗАКЛЮЧЕНИЕ: Наше исследование подчеркивает полезность систематического анализа транскриптома мозга и выделяет области белого вещества в качестве перспективной цели для дальнейших исследований ШЗ.

Keywords: *schizophrenia; long intergenic non-coding RNA; lincRNA; white matter; transcriptome; brain*
Ключевые слова: *шизофрения; длинные некодирующие РНК; дкРНК; белое вещество; транскриптом; головной мозг*

INTRODUCTION

Schizophrenia (SZ) is a neurodevelopmental disorder listed among the top 15 most burdening disabilities worldwide [1]. Despite decades of research, the etiology of the disease remains elusive due to its complexity, heterogeneity, and polygenicity. Genomic abnormalities may fractionally explain the substantial heritability of SZ but show limitations as diagnostic markers and etiology indicators due to a low fraction of explained disorder risk probability, thus suggesting a substantial role of epigenetic and environmental factors [2]. Gene expression analysis can bridge the gap between genomic and environmental risks, making it a promising approach to studying the pathophysiology of the disease.

Multiple regions in the brains of SZ patients display structural and functional abnormalities in neuroimaging studies. Yet, current molecular analysis remains restricted to a few selected brain areas. There is widespread cortical thinning in SZ individuals, with significant volumetric decreases in the frontal, temporal,

and parietal lobes [3, 4]. Several subregions of these lobes, namely the dorsolateral prefrontal cortex and the superior temporal gyrus, are routinely selected for the transcriptomic profiling of psychiatric diseases [5, 6]. Similarly, a large-scale imaging study of subcortical structures revealed smaller hippocampus, amygdala, and thalamus [7]. Consequently, multiple gene expression studies have investigated particular locations within these regions, particularly those with functional relevance to cognitive and emotional functions, but the findings have been surprisingly inconsistent [8]. Furthermore, most of the studies focused on a single region, limiting our capability to unfold the molecular networks underlying such a multiplex disorder like SZ. Furthermore, SZ-associated transcriptome alterations have been found in other "not-as-popular" parts of the brain, such as the parietal lobe [9] and the cerebellum [10, 11]. Yet, these regions are virtually neglected in psychiatric research, leaving their mechanistic involvement in SZ pathology unknown.

Long non-coding RNAs (lncRNAs) play a critical role in gene expression regulation in the brain, with disruption of this regulation implicated in various mental disorders, including SZ [12, 13]. Even though lncRNAs are usually synthesized by RNA polymerase II, similar to the protein-coding transcripts, they vastly exceed the mRNAs in terms of diversity, especially in nervous tissue [14]. Nonetheless, most of the expression analyses of post-mortem brains have focused on protein-coding RNAs, leaving the non-coding component of the transcriptome unexplored. Within the brain, many lncRNAs are specifically expressed in particular regions and at defined developmental stages [14, 15]. Therefore, alterations of lncRNA expression patterns could be affiliated with the disrupted developmental programming postulated by the neurodevelopmental hypothesis of SZ. A growing number of lncRNAs are documented to be regulators at multiple levels of gene expression affecting biological processes encompassing neuronal differentiation and the immune response [15, 16]. Due to the widespread comorbidities and substantial overlap of behavioral symptoms among psychiatric illnesses, many candidate lncRNA regulators could be connected to more than one disease [16].

The largest class of lncRNA is long intergenic non-coding RNA (lincRNAs), which, in addition to the length and non-translated requirement of lncRNA, do not overlap with protein-coding sequences. Compared to mRNAs, lincRNAs are less conserved, less efficiently spliced, and more tissue-specific despite sharing similar biogenesis pathways [17]. Aside from the overlapping features, a few other aspects support the distinction between lincRNAs and the other intragenic lncRNAs [18]. Herein, we identified lincRNAs associated with SZ and annotated their biological functions by comparing the transcriptomes of 35 anatomical regions corresponding to 10 anatomical sections in the post-mortem brains of four healthy and four SZ-diagnosed individuals (Figure 1, Table S1 in the Supplementary).

METHODS

Study design

A postmortem comparative study was conducted jointly by the Mental-health Clinic No. 1 named after N.A. Alexeev and Skolkovo Institute for Science and Technology. The inclusion criterion particular to SZ patients was: paranoid SZ (F20) diagnosed according to ICD-10. The inclusion criteria particular to the healthy control (HC) group were: no history of psychiatric or other brain-related disorders and age and sex range matching that of the SZ patient group. The inclusion criteria shared by both groups were: written informed consent for the collection of postmortem brain sample material for any type of noncommercial biological studies and anonymized processing of socio-demographic, medical, psychometric data; sudden death with no prolonged agony state from causes not directly related to brain function; and tissue collection interval shorter than 24 hours postmortem.

Brain samples

Our study used samples dissected from eight frozen human brains, four from healthy donors (HC), and four from SZ-diagnosed ones (Table S2 in the Supplementary). Post-mortem human brain samples were obtained from the National BioService Russian Biospecimen CRO, St. Petersburg, Russia. Informed consent for the use of human tissues for research was obtained in writing from all donors or next of kin by the tissue provider bank. All HC subjects were defined as healthy with respect to the sampled brain tissue by medical pathologists at the Mental-health Clinic No. 1 named after N.A. Alexeev. From each brain, we dissected 35 regions, listed in Table S1 in the Supplementary, without thawing. The dissected specimens were then preserved at −80°C until RNA extraction.

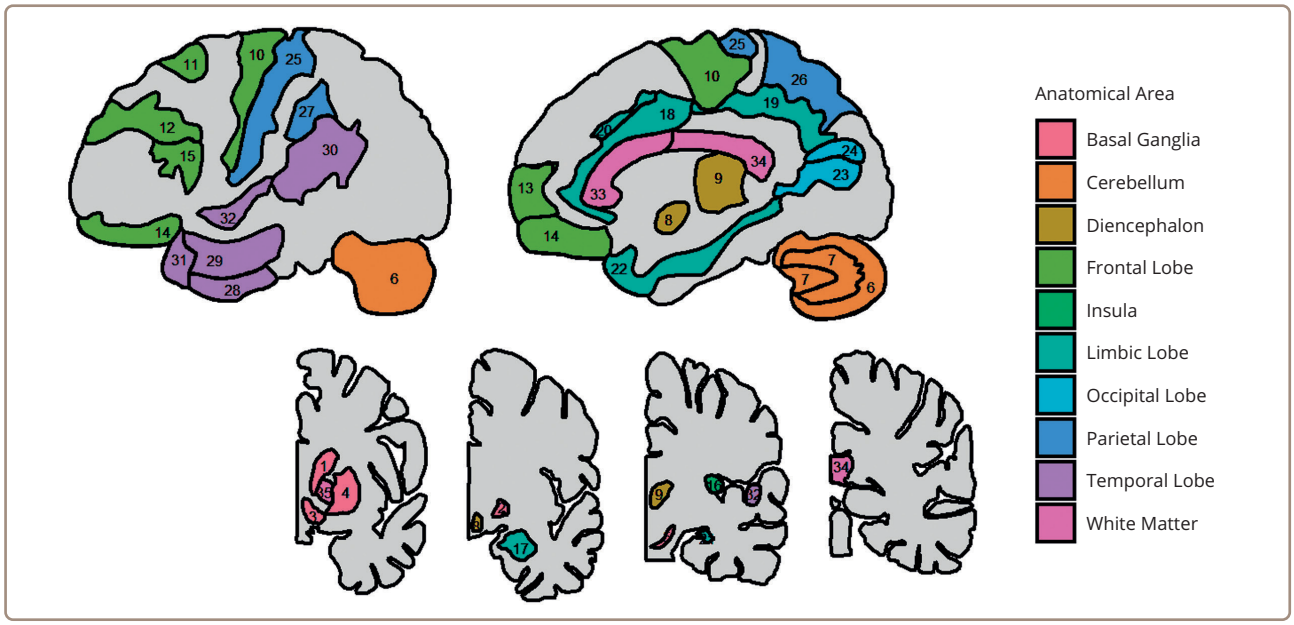

Figure 1. Schematic representation of the 35 examined human brain regions.
Note: Colors indicate the anatomical areas containing the regions. Numbers within the colored regions indicate the corresponding anatomical structures listed in Table S1 in the Supplementary.

RNA library preparation and sequencing data assessment

From each sample, RNA was extracted from an approximately 30-milligram block following the manufacturer's protocol of RNA extraction with QIAzol Lysis Reagent with no modifications [19]. After RNA integrity and concentration were measured, sequencing libraries were prepared following the manufacturer's poly-A selection protocol with no modifications [20]. The libraries were sequenced using the Illumina Hiseq 4000 platform.

FastQC [21] was used to assess the quality of raw reads. We used Trimmomatic [22] to remove low-quality reads and all adapters identified previously or provided by Trimmomatic. We mapped the reads to the human reference genome GRCh38 with HISAT2 [23]. The gene count matrix representing gene expression values was retrieved as transcripts per million (TPM) using Stringtie [24]. Gene annotations were obtained from Ensembl v91 [25].

Differential gene expression analysis

Genes identified as long intergenic non-coding RNAs (lincRNAs) and protein-coding (mRNAs) according to Ensembl annotation were chosen for downstream analysis. For both the control and disease samples, we only considered the genes with no more than two zero coverage values among eight samples representing each region (two-zero threshold). The TPM count data were transformed to the logarithmic scale using the package *DESeq2* [26]. We adjusted the expression levels for the sample quality using the linear regression analysis with RIN (RNA Integrity Number) values. Finally, we used donor-centered normalization for each individual by subtracting the means of log-transformed expression values calculated based on expression of the 35 regions of a given brain from the regional expression values of the respective individual. We conducted the Principle Component Analysis to visualize the variation among 280 examined brain samples using the donor-normalized expression levels of 861 detected lincRNAs. Based on the regional means of pooled HC and SZ groups, we identified three clusters of brain regions using the hierarchical clustering method, in which distances were calculated as one minus Pearson correlation coefficients and clusters were defined by the Ward's linkage function.

For the lincRNAs dataset, Levene's test was used to exclude genes with high heteroscedasticity (the threshold for exclusion was p <0.05) yielding 768 detected variation-balanced lincRNAs. Two-way ANOVA including the effect of region and conditions (diagnosis) conducted based on donor-normalized RIN-corrected $\log_{10}$-transformed TPM values was used to identify transcripts with significant differences for the interaction terms (p <0.05 after Benjamini–Hochberg correction). These transcripts were chosen for the *post hoc* Tukey test. Differentially

expressed lincRNAs (DELs) were defined as those with significant difference between the two conditions in the Tukey test in at least one brain region. The fold changes within a region were measured by subtracting the mean transformed expression of the control groups from that of the SZ groups. We defined upregulated DELs as the ones showing higher expression in SZ brains compared to the controls and downregulated DELs as the ones showing an opposite expression behavior.

Enrichment analysis

We calculated the Pearson correlation between the donor-normalized RIN-corrected $\log_{10}$-transformed TPM expression values of DELs and all mRNAs passing the two-zero threshold described above. Protein coding genes with a correlation coefficient $r \geq 0.85$ were defined as potential targets of the respective DELs. DELs with at least 10 targets were used for downstream analyses. For each DEL, we analyzed the enrichment of its targets using all coding genes passing the detection threshold as the background set. Gene Ontology (GO) terms, Kyoto Encyclopedia of Genes and Genomes (KEGG), and Reactome pathways analyses for all groups were implemented using the clusterProfiler R package [27]. Terms and pathways with an adjusted p-value <0.05 were considered enriched.

We compiled a set of marker genes for each of the eight main brain cell types based on published gene sets. For excitatory and inhibitory neurons, we chose intersections of the corresponding sets from the studies in [28, 29]. Similarly, other neuron markers, microglia, astrocytes, and oligodendrocytes represented the respective intersections of lists reported in [28, 30, 31]. Markers for oligodendrocyte progenitor cells were reported in [28], and the ones for endothelial cells were extracted from [29]. We tested the overrepresentation of these markers in the list of DEL targets using Fisher's exact test, followed by Benjamini-Hochberg correction.

RESULTS

Region-dependent lincRNA expression differences cluster in white matter regions of the brain

Previously, we published transcriptome data covering 33 regions of a healthy human brain [28]. Here, we analyzed gene expression in the same 33 regions in four individuals diagnosed with SZ, and two additional brain regions, temporopolar cortex (BA38) and secondary auditory anterior cortex (BA21a), in the diagnosed and control groups (Figure 1, Table S1 in the Supplementary). Based on these data, we detected the expression of 861 annotated human lincRNAs that passed the intensity threshold. Visualization of expression variation using the principal component analysis (PCA) showed substantial overlap of HC and SZ samples (Figure 2A), while the segregation of the samples with regard to anatomical regions was more evident (Figure 2B).

Aligning with the PCA results, we identified three clusters of brain regions produced by unsupervised hierarchical clustering based on lincRNA expression levels, aligning with the anatomical subdivision of the brain (Figure

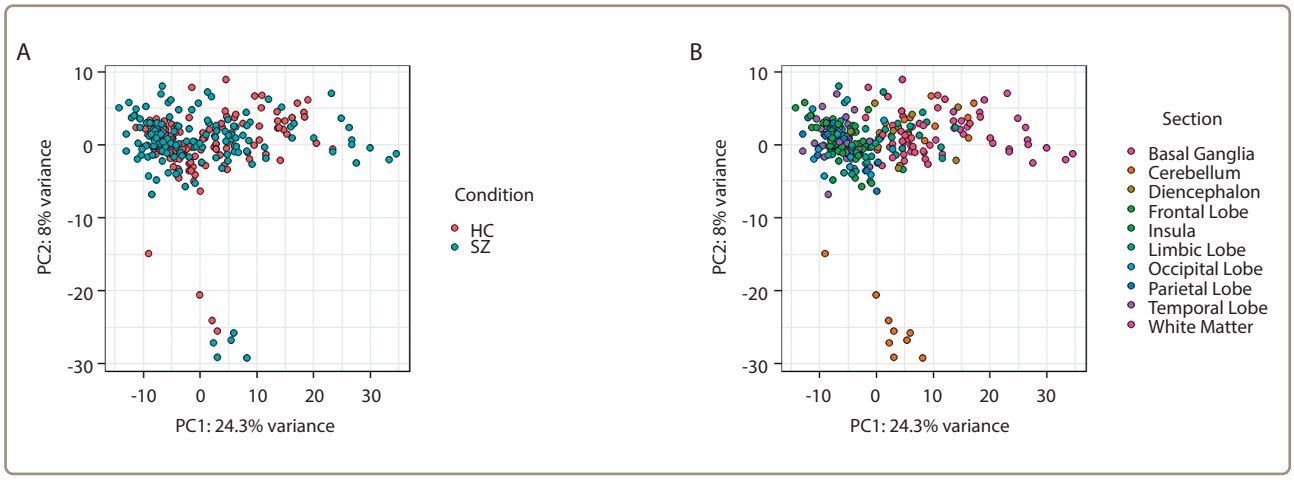

Figure 2. Global patterns of lincRNA expression in the human brain.

Note: (A, B) PCA showing lincRNA expression-based differences among 280 examined brain samples colored by condition (A) or anatomical subdivision (B). Each dot represents a brain sample.

3, Figure S1 in the Supplementary). The first cluster contains mainly the neocortical areas; the second — all the connective nerve tracts and the cerebellum; and the third — the diencephalon and most of the basal ganglia. Substructures of the limbic system belong to both clusters I and III, with the regions spatially related within the clusters.

Out of 861 detected lincRNAs, the expression of 135 depended significantly on both conditions and brain regions (two-way ANOVA, Benjamini–Hochberg (BH)-adjusted p <0.05 for the interaction term, excluding 93 genes with unequal variance). Among these lincRNAs, we identified 37 DELs showing differences between HC and SZ individuals significant in at least one individual brain region (Tukey test, p <0.05; Figure 4A, Table S3 in the Supplementary). Of them, four DELs were dysregulated in two regions, while the rest were dysregulated in one. Further, 31 of the 37 DELs showed a two-fold or greater expression level difference between the two conditions (Table S3 in the Supplementary). Notably, these significant differences were not distributed uniformly within the brain but were associated with 10 out of the 35 examined regions. Most of the associations were found in the regions containing connective axonal tracks: cerebellar white matter contained two down- with 14 up-regulated lincRNAs and three regions of the cerebral white matter contained 13 down- with seven up-regulated lincRNAs (Figure 4B).

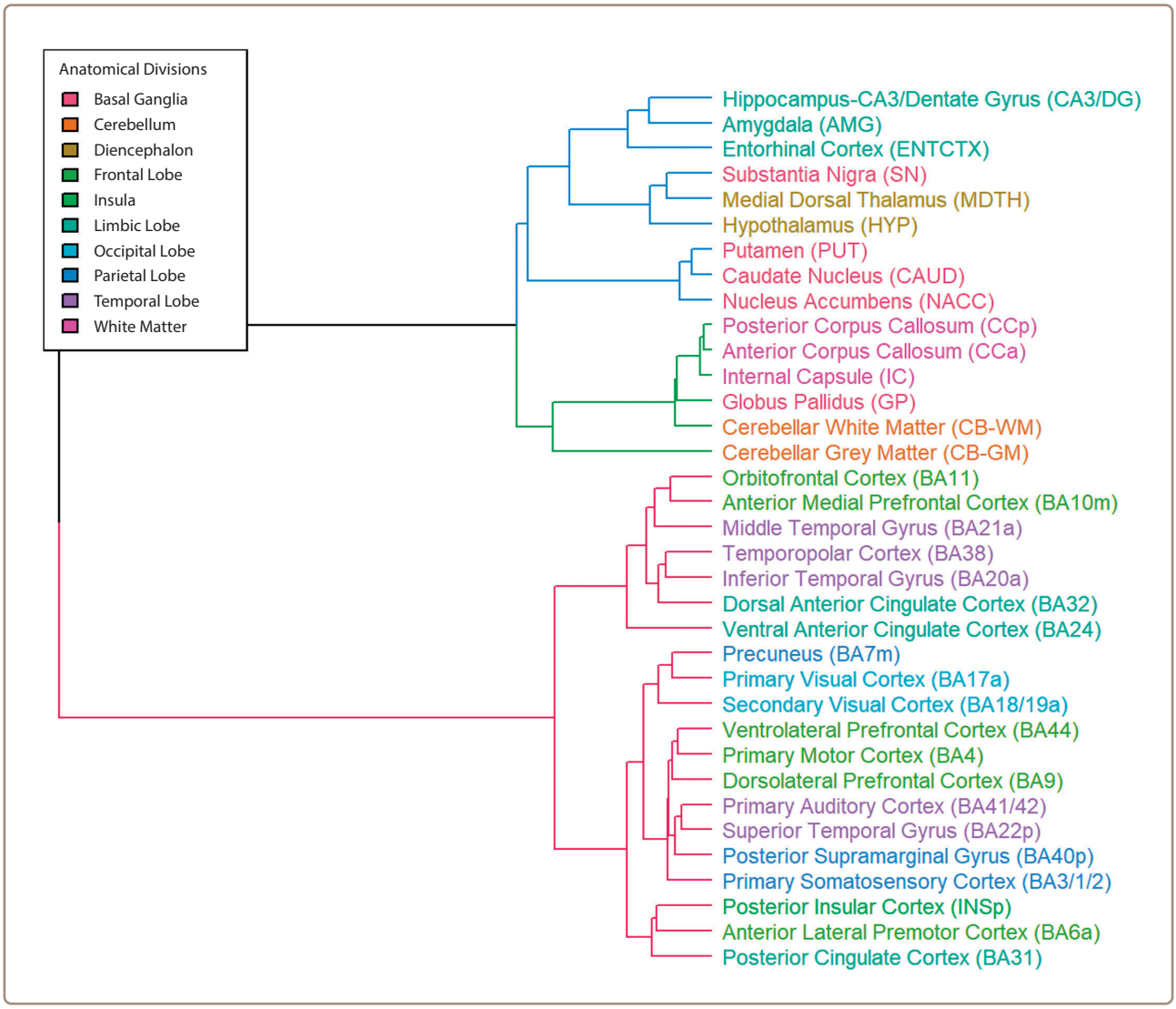

Figure 3. Unsupervised hierarchical clustering of brain regions based on the donor-normalized expression profiles of 861 lincRNAs averaged across HC and SZ samples.

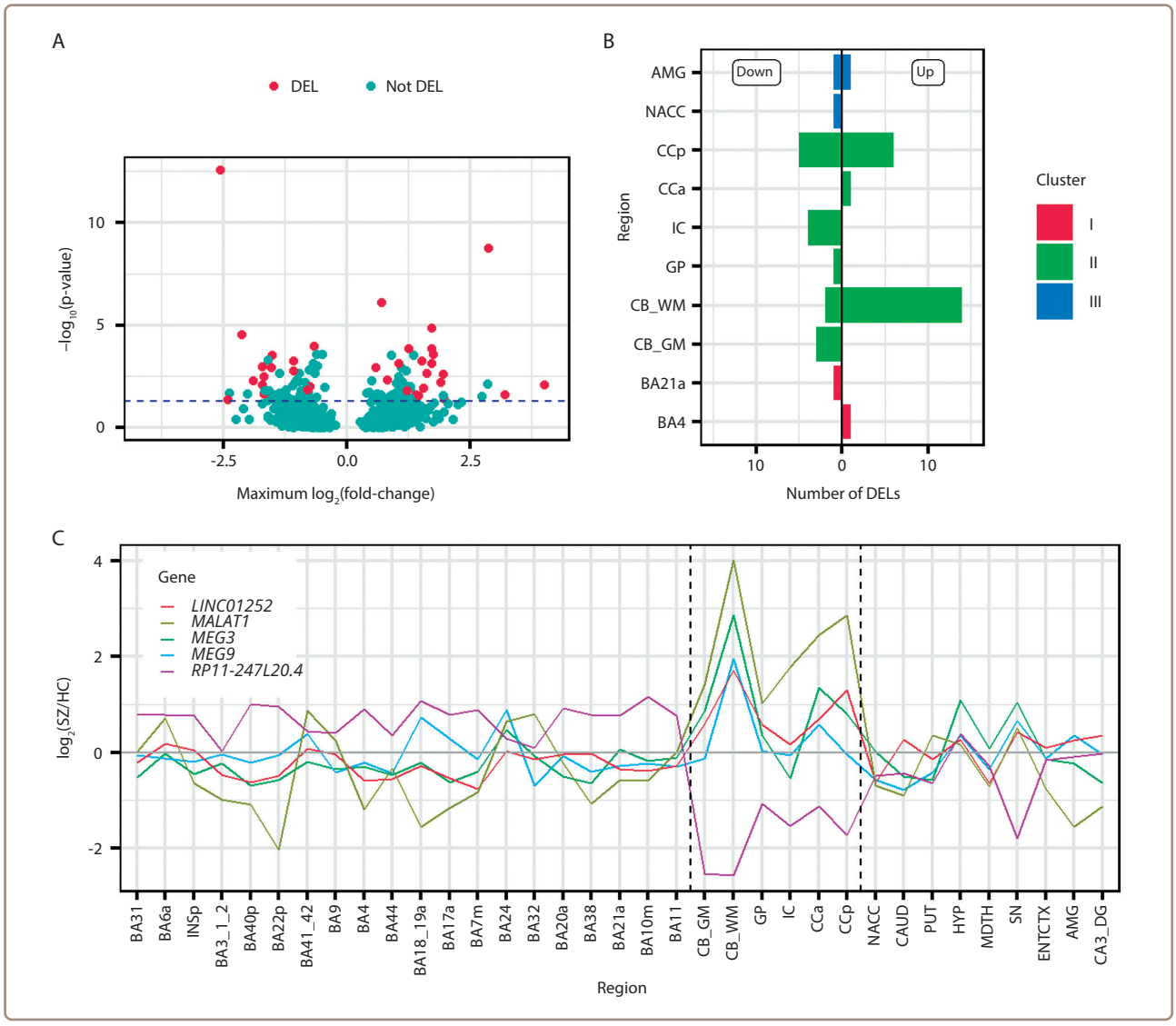

Figure 4. Differentially expressed lincRNAs (DELs) and the corresponding brain regions.
Note: (A) A volcano plot showing 768 lincRNAs used in ANOVA with 37 DELs marked. The vertical axis shows the ANOVA BH-corrected p-value for the region-diagnosis interaction term. The dashed blue line indicates the threshold p=0.05. The plotted fold-change values represent the maximum fold-change among 35 regions for each lincRNA. (B) The number of down- and up-regulated DELs identified in each of the 10 brain regions containing at least one significant expression difference. Colors represent the brain region clusters shown in Figure 2C. (C) The profiles of the difference between the SZ and HC expression levels drawn for five DELs having the lowest SZ/HC comparison p-value, previously reported in the literature as SZ-associated, or both. The dashed black lines delineate the brain region cluster containing white-matter-rich regions.

The DELs showing the most significant difference between SZ and HC expression in our study included the following transcripts: *MEG3*, *RP11-247L20.4*, and *LINC01252*. These lincRNAs were all dysregulated in the white matter of the cerebellum, and *RP11-247L20.4* was also significantly downregulated in the cerebellar gray matter. We illustrated the expression profiles of these five genes in Figure 4C. Notably, *MALAT1* was also the gene with the biggest difference amplitude among DELs, showing a 16-fold increase in the cerebellum of SZ patients compared to HC individuals.

Re-analysis of published lincRNA data sets revealed a positive and significant correlation of SZ-associated fold changes between our data and published lincRNA ones in the amygdala (two studies, Spearman correlation test, p >0.45, p <0.03) [32, 33] but not in the dorsolateral prefrontal cortex (one study, Spearman correlation test, p=0.15, p=0.39) [34] (Table S4 in the Supplementary).

Functional annotation of DELs links them to neuroplasticity and neurotransmission

While human protein-coding genes tend to have substantial functional annotation, this is not the case for the vast majority of lincRNA. Nonetheless, the co-expression of mRNA and lincRNA transcripts could be an indication of the functional roles of non-coding counterparts. To perform such an annotation, we defined mRNAs strongly correlated with a DEL expression difference profile as potential targets of the respective DEL. Whilst most DELs had few or no targets, three DELs correlated with outstanding numbers of mRNAs, which altogether constituted 218 out of the 231 identified DEL-mRNA correlations. These three DELs included *RP11-74E22.8* lincRNA upregulated in the cerebellar white matter and *LINC01963* and *RP11-416I2.1,* both downregulated in the internal capsule, as well as a white matter region. Furthermore, the profiles of *RP11-74E22.8* and *LINC01963* were strongly positively correlated (Pearson r=0.76) and they shared 17 common mRNA targets out of 71 and 105 targets, respectively.

The potential mRNA targets of the three DELs were significantly associated with the neuronal activity terms listed in the GO database (hypergeometric test, BH-adjusted p-values <0.05). Specifically, mRNA targets of *RP11-416I2.1* were associated with voltage-gated channels and neuroplasticity, while targets of the other two DELs were linked to synaptic transmission and signaling terms (Figure 5A, Figures S2A, S2B in the Supplementary). Analysis of mRNA target enrichment using another functional annotation database, the KEGG [35], linked four pathways, including the "synaptic vesicle cycle" and "metabolism of alanine, aspartate, and glutamate", with targets of *LINC01963* (Figure S2B in the Supplementary). Functional annotation using Reactome Knowledgebase [36] yielded similar results:

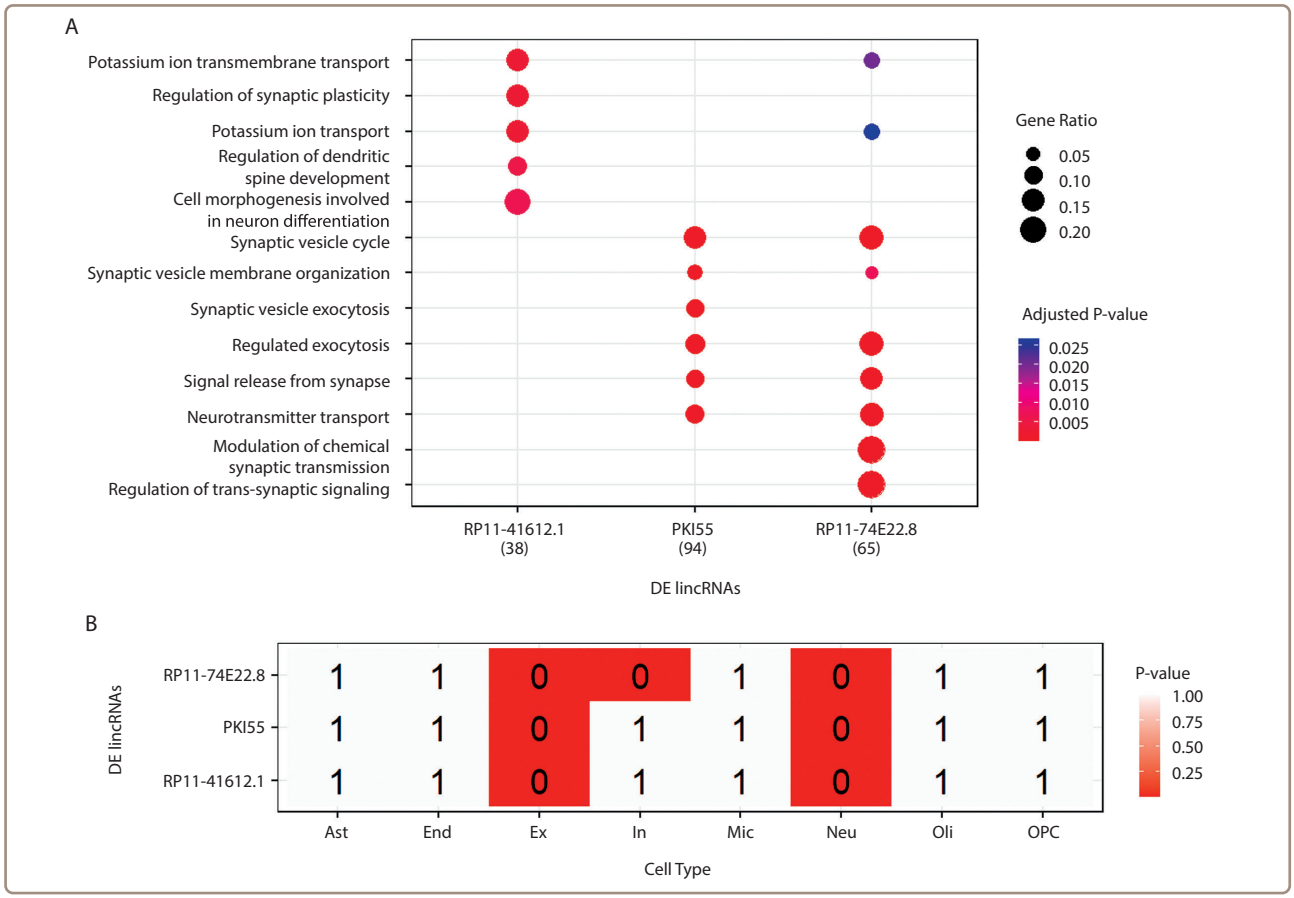

Figure 5. Annotation of three lincRNAs with the highest number of correlated mRNAs.
Note: (A) Top GO biological process terms enriched in each target group. (B) Brain cell type markers enriched in each target group. Ast: Astrocyte, End: Endothelium, Ex: Excitatory neuron, In: Inhibitory neuron, Mic: Microglia, Neu: Neuron, Oli: Oligodendrocyte, OPC: Oligodendrocyte progenitor cell.

the targets of *RP11-416I2.1* were enriched in potassium channels and G-protein-coupled receptors, while the other two target groups shared mutual entries related to the neurotransmitter release cycle (Figure S2D in the Supplementary).

We further investigated the association of DEL target mRNAs with eight main brain cell types by testing them using a customized list of marker genes extracted from publications. The analysis revealed an evident and significant association between the targets of all three target-rich DELs and general neuronal markers, as well as markers of excitatory neurons (Figure 5B). This result aligns with the functional annotation outcome dominated by terms related to neuronal functionality. In addition, the targets of *RP11-74E22.8* overlapped significantly with inhibitory neuron markers, which might be related to their enrichment in the GABA, dopaminergic, and norepinephrine pathways. These results suggest that the three DELs could modulate a network of genes expressed in neurons and involved in synaptic signal transduction.

DISCUSSION

Our analysis of lincRNA expression in the SZ patients' brains revealed few alterations in the cerebral cortex and basal ganglia regions commonly thought to be associated with the disorder. Instead, it shows substantial lincRNA dysregulation in the cortical white matter regions and the cerebellum. Our study defers from most of the previous SZ brain expression analyses in two substantial aspects. First, by measuring gene expression in multiple regions of the same brain, we based our analysis on the expression profiles of the transcripts within the brain, thus minimizing any interindividual variation. This approach allowed us to focus on the expression differences particular to specific brain regions, including the ones neglected by previous studies. Interindividual variation poses a serious problem in human studies due to uncontrollable and diverse genetic and environmental factor effects, resulting in the loss of biologically meaningful differences with marginal to modest effect sizes [37]. Most existing gene expression studies of the SZ brain focus on either a single or a few regions of the cerebrum [8]. However, sporadic omics screening of the neglected brain regions, such as the transcriptome and proteome assessment of the cerebellum [10, 11], have reported meaningful expression alterations. In this study, focusing on the expression alteration patterns recorded across the 35 brain regions, we show that the white matter and the cerebellum might warrant more attention in future SZ studies.

The main components of the white matter are myelinated axons extending from the neuronal cell bodies. Thus, it might seem unusual that the observed lincRNA expression alterations were not accompanied by changes in the corresponding gray matter. One hypothesis is that the changes in the gene expression of these regions arose mainly from local glial cells. This notion, however, is unlikely to hold for the cerebellum gray matter, given that the non-neuronal cells account for less than one-fifth of the total cell population in this structure [38]. Thus, gene dysregulations in glial cells have to be substantial in order to explain the observed differences. Another possible explanation of the observed differences is the redistribution of transcripts leading to the accumulation of the DELs in axons, possibly due to molecular transport impairment. This explanation aligns with the white matter pathology of SZ [39] and could be linked to a transcriptomic study of the cerebellum reporting dysregulation of the genes involved in the Golgi function and presynaptic vesicular transport in SZ [11]. Alternatively, the disconnected patterns of white matter regions and the cerebellum from the rest of the brain could be a consequence of cell-type-specific expression. There are many nuclei in the cerebellar and cerebral cortices, including all of the cerebellar granular layer neurons, that do not project into the other brain regions. Thus, the transcriptomes of such non-projecting neurons might not be reflected in the white matter transcriptome. Future experiments should investigate the cellular locations of these molecules to uncover the underlying mechanism and clarify these speculations.

The second particular aspect of our study is its focus on non-coding RNA expression. Unlike mRNA, lincRNA expression displays more pronounced tissue and brain region specificity, as well as greater response amplitudes, making them better perspective markers of disorder-related alterations [40]. On the other hand, the evident drawback of the lincRNA research is an almost complete lack of functional annotation, hindering results interpretation. In our study, however, we were able to largely overcome this limitation by taking advantage of a lincRNA-mRNA co-expression analysis relying on the transcript profiles measured across the 35 brain regions. The reliance on these profiles, instead of the variation-prone inter-individual

comparisons, allowed us to unambiguously assign co-expressed lincRNA targets to neurons and neuron-specific functions, such as synaptic signal transduction. It is also noteworthy that a substantial fraction of the DELs identified in our study overlapped with lincRNAs previously reported by the few corresponding analyses. At the level of individual lincRNA, *MEG3* has been previously reported to be differentially expressed in the hippocampus [41], superior temporal gyrus [42], and amygdala [32, 43] of SZ patients. Similarly, *LINC01252* has been reported to be upregulated in SZ in the amygdala [33]. Two other DELs that have appeared in the related literature included *MEG9* dysregulation in the amygdala [32] and *MALAT1* — in the dorsolateral prefrontal cortex [34]. The direction of effect reported for these lincRNAs coincided with the one found in our analysis, with the sole exception of the *MEG3* expression difference in the hippocampus, where the difference was not statistically significant in our study. Besides particular lincRNAs, three published studies contained lincRNA datasets: two from amygdala and one from prefrontal cortex [32–34]. While the agreement of our results with the reported amygdala differences was significant, in the cortex we only detected a positive correlation trend. The absence of a statistically significant agreement in the prefrontal cortex could be due to insufficient power of the comparison and, more importantly, lack of substantiation of lincRNA expression alterations in this region. Our general analysis, as well as the expression profiles of the five selected DELs, shows the concentration of large-amplitude SZ-associated expression differences in white matter regions and cerebellar gray matter, with some significant differences also found in the amygdala, but none in the prefrontal cortex. These preliminary findings support further confirmative research focusing on disease-associated non-coding RNA.

The main limitation of our work is the low count of investigated brains per group. Although our study included 35 regions from each individual and the number of samples per group was balanced, we had only four biological replicates in each group. This number is certainly low for such a heterogeneous disease as SZ. The clinical presentation of SZ is highly diverse, so whether the subjective, behavior-based diagnosis of the disease agrees with the pattern of molecular alterations remains a topic of controversy [44]. However, this limitation is universal and represents a problem largely unresolved in most post-mortem brain studies [2, 8]. Unlike other studies, our analysis minimizes inter-individual variation by using the average expression level of each transcript within a given brain as an internal control. As a result, despite the limited sample size, we identified numerous DELs whose involvements in SZ could be supported by previous SZ studies, as well as their evident association with the mRNA transcripts involved in neuronal-specific functionality, suggesting biologically meaningful signals.

CONCLUSION

Our analysis of long, non-coding RNA expression patterns across 35 diverse brain regions reveals the clustering of SZ-associated expression alterations in brain structures routinely neglected by transcriptome studies: white matter and cerebellar brain regions. Further, the identified lincRNA expression alterations were associated with mRNA preferentially expressed in neurons and involved in neuron-specific functions, such as synaptic transmission. These results strongly indicate that further studies of SZ molecular mechanisms should involve a broad selection of brain structures, including the white matter regions and cerebellum.

Article history:
Submitted: 09.10.2022
Accepted: 07.11.2022
Published Online: 07.12.2022

Acknowledgments: We thank all authors for their contributions to the research.

Authors' contribution: A.Yu. Morozova, Ya.A. Zorkina, D.S. Andreyuk — performed clinical diagnostic assessment of the SZ patients and curated the brain sample collection; O.I. Efimova — carried out brain sample dissection; T. Nguyen, A.V. Tokarchuk — performed formal analysis; T. Nguyen, Ph.E. Khaitovich — wrote the manuscript; G.P. Kostyuk, Ph.E. Khaitovich — designed the study and supervised the work. All authors read and approved the final manuscript.

Funding: This work was supported by the Russian Science Foundation under grant No. 22-15-00474.

Conflict of interest: The authors declare no conflicts of interest.

Supplementary data

Supplementary material related to this article can be found in the online version at doi: 10.17816/CP219

For citation:

Nguyen T, Efimova OI, Tokarchuk AV, Morozova AYu, Zorkina YaA, Andreyuk DS, Kostyuk GP, Khaitovich PhE. Dysregulation of long intergenic non-coding RNA expression in the schizophrenia brain. Consortium Psychiatricum 2023;4(1):CP219. doi: 10.17816/CP219

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Treatment of Depression with Vortioxetine and Second Generation Antipsychotics During the Period of Remission Formation in Schizophrenia (Interim Data Analysis)

Комбинированное лечение депрессии вортиоксетином и антипсихотиками второго поколения в период формирования ремиссии при шизофрении (данные промежуточного анализа)

doi: 10.17816/CP3728

Original research

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ABSTRACT

BACKGROUND: Depression in patients with schizophrenia worsens the course of the disease by increasing the risk of suicide, by complicating the clinical picture of the disorder, and by reducing the quality of the social functioning; its treatment is difficult, since monotherapy, even when involving modern antipsychotics, does not always prove successful. While the prescription of additional antidepressants (ADs) can improve the likelihood of a better outcome, the effectiveness of such augmentation in many cases is yet to be proven. Therefore, it is still important that one weighs the effectiveness of various combinations between most of the known ADs and some second-generation antipsychotic (SGA) in the treatment of depression that occurs at different stages of schizophrenia. In previous studies, the use of vortioxetine as an adjunct to an antipsychotic yielded a reduction in negative symptoms, a clinically significant improvement in cognitive functions that differed from its antidepressant effect, and good tolerability, which affects how committed to treatment a patient remains.

AIM: To study the changes that occur over time in the clinical manifestations of depression, negative and cognitive impairment, as well as the social adequacy of patients receiving a combination therapy with second-generation antipsychotics and vortioxetine, which were prescribed in real clinical practice at doses approved in the Russian Federation.

METHODS: We performed a comparative analysis of the changes in depression symptoms and negative symptoms, cognitive impairment, as well as function of 78 patients with severe manifestations of depression at the stage of exacerbation reduction and subsequent remission of paranoid schizophrenia. Combination treatment with SGA and vortioxetine was used in 39 patients, and 39 patients who had similar clinical manifestations received just SGA. During the observation period, the mental disorder severity and depression symptom severity were assessed 3 times (before the start of treatment, after three months, and after six months) using the Clinical Global Impression (CGI) scale and Calgary Depression Scale for Schizophrenia (CDSS), respectively; patients were also assessed using the Negative Symptoms Assessment-5 (NSA-5) scale, Perceived Deficits Questionnaire-20 items (PDQ-20) scale, and Personal and Social Performance (PSP) scale.

RESULTS: According to the ANOVA results, by the end of the observation period, patients, regardless of their therapeutic group, showed a statistically significant decrease in the level of depression on the CDSS scale, the severity of negative symptoms on the NSA-5 scale, cognitive symptoms on the PDQ-20 scale, as well as an improvement in personality and society, judging by the increase in the total PSP scores. There were also significant differences between the compared main (SGA + vortioxetine) and control (SGA) groups in terms of the changes in the total score on the CDSS and PSP scales. An interesting aspect of the changes in the clinical scores was a noticeable improvement in the SGA + vortioxetine group after 3 months of treatment, in the absence of a similar improvement in the control group, and the achievement of approximately the same scores in both groups after 6 months. In particular, there were significant differences between the SGA + vortioxetine and SGA groups in terms of the mean CDSS (p <0.001), NSA-5 (p=0.003), PDQ-20 (p <0.001), and PSP (p=0.004) scores after 3 months. Analysis of the time before early withdrawal from the study showed that significantly more patients in the SGA + vortioxetine group completed the study program (n=27, 69.23%) compared with the SGA group (n=13, 33.33%) (χ^2 =14.618, df=1, p <0.001, log-rank test. The mean survival time in the SGA group was significantly (p <0.001) less and amounted to 101.436 days (95% CI: 81.518–121.354), and in the SGA + vortioxetine group it amounted to 161.744 days (147.981–175.506). The relative risk of full study completion in the vortioxetine + SGA group compared with that in SGA was 3.618 (1.871–6.994).

CONCLUSION: The addition of vortioxetine to the SGA therapy accelerates the reduction of the depression symptoms that occur at the stage of psychosis regression and early remission, contributes to the accelerated reduction in negative symptoms, positively affects the subjective assessment of cognitive impairment severity, and has a significant positive effect on the level of psychosocial functioning.

АННОТАЦИЯ

ВВЕДЕНИЕ: Депрессия у больных шизофренией ухудшает исходы болезни, повышая риск самоубийств, осложняя клиническую картину и снижая качество социального функционирования; ее лечение затруднено, так как монотерапия даже современными антипсихотиками не всегда успешна, а назначение дополнительных антидепрессантов (АД) может улучшать результат, но эффективность такой аугментации во многих случаях еще требует доказательств. Поэтому до сих пор остается актуальным анализ эффективности комбинаций большинства АД и антипсихотика второго поколения (АВП) при лечении депрессии, возникающей на разных этапах шизофрении. В ранее проведенных исследованиях назначение вортиоксетина в качестве дополнения к антипсихотику показало уменьшение выраженности негативных симптомов, клинически значимое улучшение когнитивных функций, которое отличался от его антидепрессивного действия, а также хорошую переносимость, что влияет на приверженность лечению.

ЦЕЛЬ: Изучение динамики клинических проявлений депрессии, негативных и когнитивных нарушений, а также социального функционирования пациентов на фоне комбинированной терапии АВП и вортиоксетином, которые назначались в условиях реальной клинической практики в разрешенных в Российской Федерации дозах.

МЕТОДЫ: Проведен сравнительный анализ динамики депрессивной и негативной симптоматики, когнитивных нарушений, а также личностного и социального функционирования у 78 пациентов с выраженными проявлениями депрессии на этапе редукции обострения и последующего становления ремиссии параноидной шизофрении. Лечение комбинацией АВП и вортиоксетина получали 39 человек, а 39 пациентов, имевших аналогичные клинические проявления, получали монотерапию АВП. В период наблюдения 3 раза (до начала лечения, спустя три месяца и шесть месяцев) проводилась оценка тяжести психического расстройства по шкале общего клинического впечатления (Clinical Global Impression, CGI), выраженности депрессивной симптоматики по шкале депрессии Калгари (Calgary Depression Scale for Schizophrenia, CDSS), а также пациенты оценивались по 5-пунктовой шкале негативной симптоматики (5-Items Negative Symptoms Assessment, NSA-5), по 20-пунктовой шкале субъективно воспринимаемого когнитивного дефицита (Perceived Deficits Questionnaire-20 items, PDQ-20) и по шкале личностного и социального функционирования (Personal and Social Performance, PSP).

РЕЗУЛЬТАТЫ: Данные проведенного теста ANOVA свидетельствуют, что вне зависимости от терапевтической группы у пациентов к завершению периода наблюдения отмечались статистически значимое снижение уровня депрессии по шкале CDSS, выраженности негативных симптомов по шкале NSA-5, когнитивных симптомов по шкале PDQ-20, а также улучшение личностного и социального функционирования — повышение итогового балла шкалы PSP. Вместе с тем, между сравниваемыми основной (АВП + вортиоксетин) и контрольной (АВП) группами выявлены статистически значимые различия по динамике суммарного балла по шкалам CDSS и PSP. Особенностью динамики показателей клинических шкал стало наличие заметного улучшения в группе АВП + вортиоксетин через 3 месяца лечения при отсутствии аналогичного улучшения в группе контроля и достижение примерно одинаковых значений шкал в обеих группах через 6 месяцев. В частности, через 3 месяца между группами АВП + вортиоксетин и АВП имелись статистически значимые различия средних значений шкал CDSS (p <0,001), NSA-5 (p=0,003), PDQ-20 (p <0,001) и PSP (p=0,004). Анализ времени до преждевременного завершения исследования продемонстрировал, что в группе АВП + вортиоксетин статистически значимо больше пациентов полностью завершили программу исследования (n=27, 69,23%) по сравнению с группой АВП (n=13, 33,33%) (χ^2 = 14,618, df = 1, p <0,001, лог-ранк текст). Коэффициент выживаемости (коэффициент времени, в течение которого пациент продолжает назначенную терапию) в исследовании в группе АВП было статистически значимо (p <0,001) меньше и составило 101, 436 дня (95% ДИ: 81 518–121 354), а в группе АВП + вортиоксетин — 161 744 дня (147 981–175 506). Показатель относительного риска для полного завершения исследования в группе вортиоксетин + АВП по сравнению с АВП составил 3618 (1871–6994).

ЗАКЛЮЧЕНИЕ: Присоединение вортиоксетина к терапии АВП позволяет ускорить редукцию симптомов депрессии, возникающих на этапе обратного развития психоза и становления ремиссии, способствует ускоренному ослаблению негативных симптомов, положительно влияет на субъектную оценку выраженности когнитивных нарушений, оказывает существенное положительное влияние на уровень психосоциального функционирования.

Keywords: *depression; negative symptoms; cognitive impairment; exacerbation of schizophrenia; schizophrenia; second-generation antipsychotic; psychopharmacotherapy; psychosocial functioning; vortioxetine*
Ключевые слова: *антипсихотик второго поколения; вортиоксетин; депрессия; негативные симптомы; когнитивные нарушения; психофармакотерапия; психосоциальное функционирование; ремиссия шизофрении; шизофрения*

INTRODUCTION

Approximately 80% of patients with schizophrenia suffer from depression or a history of depression [1]. Thus, depression symptoms were recently included amongst the main symptoms to watch for and added as one of the telltale signs of schizophrenia spectrum disorders [1–5]. Affective symptoms in schizophrenia are no longer believed to be signs of a good prognostic, since patients with a high level of affective disorders appear more at the "bipolar" rather than the deficit/autistic extreme of the psychosis continuum [6]. In fact, depression is associated with worse outcomes in schizophrenia [7, 8]. It increases the likelihood of a transition from a state of ultra-high risk of psychosis to the first psychotic episode [9]. Patients with schizophrenia compounded by depression tend to be more susceptible to drug abuse, complain of poorer quality of life, mental condition, frayed family relationships, and are less likely to stick to their treatment regimen; they are significantly more likely to relapse and threaten their own safety and that of others — including through violence — be susceptible to arrest, victimization, and suicide [10]. Depression in schizophrenia is a more significant factor in determining whether a patient is contemplating suicide than even the influence of imperative hallucinations [11], with suicidal thoughts occurring in 63% of such patients [7]. Depression in the prodromal phase of psychosis appears to be the most significant predictor of future depression and cases of self-aggression [7]. The combination of even attenuated psychotic experiences and a mild depressive disorder is associated with suicidal behavior; i.e., a patient does not need to suffer from severe depression or severe psychosis to display suicidal behavior [12].

Depression not only complicates the course of schizophrenia, but it also creates additional difficulties in differential diagnosis. In particular, symptoms of depression in patients with schizophrenia are associated with cognitive impairment [13]. In practice, manifestations of depression are difficult to distinguish from negative symptoms [14, 15]. In particular, it is difficult to determine whether such symptoms as anhedonia, mental anesthesia, and emotional indifference, loss of motivation, anergy, flattened affect, social isolation, ideational retardation, and impoverishment of thinking denote depression or are negative manifestations of schizophrenia [1, 15, 16]. It is often difficult to distinguish between signs of depression and catatonia [17, 18]. It can be difficult to assess the nature of the relationship between depressive and psychotic manifestations: on the one hand, depression often occurs during an exacerbation of schizophrenia; on the other hand, severe depression is characterized by psychotic symptoms [13, 16].

Despite the fact that depression is recognized as one of the aspects of the psychopathology of schizophrenia, its treatment still presents challenges and is not always scientifically justified [1, 19]. Thus, AD has been used on a rather pragmatic basis for many decades [1] and about a third of patients with schizophrenia are treated with AD in an outpatient setting [20]. It has been over 20 years since Samuel G. Siris recommended switching to SGA monotherapy for the treatment of depression in schizophrenia [21], and it can already be argued that the expectations placed in the strategy have not been fully borne out. Despite the widespread use of SGAs, and the proven antidepressant effects of many of them [21, 22], the prevalence of depression in schizophrenia remains high and suicide rates have not changed, indicating the need for more treatment options [1]. The randomized controlled studies (RCSs) conducted so far and a meta-analysis of the effectiveness of AD in the treatment

of depression in schizophrenia showed the following: the combination of AD and SGA was moderately more effective than SGA monotherapy in relation to depressive, negative, and even positive symptoms, as well as quality of life; the effect on depressive and negative symptoms was more pronounced when the criterion for prescribing AD was minimum severity of these symptoms; there were no significant differences in the risk of psychosis exacerbation, premature discontinuation of medication, and the number of participants that continued therapy between those receiving a combination therapy of AD and SGA and a control group receiving SGA monotherapy [23]. However, so far, the effectiveness of many ADs in the treatment of depression associated with schizophrenia remains unclear or unproven. Finally, despite the addition of AD to the treatment regimen, depressive symptoms persist in a large proportion of patients [19, 23].

Let's summarize the above: depression in patients suffering from schizophrenia worsens the outcome of the disease by increasing the risk of suicide, complicating the clinical picture, and reducing the quality of the social functioning; its treatment is difficult, since monotherapy, even with modern antipsychotics, is not always successful and prescription of AD can improve the outcome, but the effectiveness of such augmentation in many cases is yet to be proven. Therefore, it is important to analyze the effectiveness of combinations of most ADs and SGA in the treatment of the depression that occurs at different stages of schizophrenia. Vortioxetine was chosen for this study, because, in previous studies, the use of vortioxetine as an adjunct to an antipsychotic showed a reduction in negative symptoms [24], a clinically significant improvement in cognitive functions that differed from its antidepressant effect [25], the ability to improve the condition of patients resistant to treatment [26], and good tolerability, which affects adherence to treatment [25]. In addition, even earlier, in numerous RCSs with the inclusion of large samples of patients and in a meta-analysis, vortioxetine, along with its antidepressant effects, showed a direct pro-cognitive effect and, according to some data, an associated beneficial effect on social functioning and quality of life during treatment of the major depressive disorder [27–40]. Its ability to clearly improve a number of cognitive parameters (quality of attention, concentration, orientation, executive functions, speed of psychomotor reactions, delayed recall) makes vortioxetine different from most ADs [33, 41–43]. The cognitive improvement is supposed to be due to both a vortioxetine-induced increase in serotonin (due to inhibition of the serotonin transporter) and direct modulation of serotonin receptors, especially the 5-HT_3 block, which causes an increase in the hippocampal transmitters: glutamate, acetylcholine, and norepinephrine [32, 41].

The aim of the study was to assess the changes in the psychosocial functioning of schizophrenic patients with early remission during vortioxetine therapy, which was prescribed in addition to the main therapy with one of the SGAs: quetiapine, olanzapine, paliperidone, or risperidone.

The objectives of the monitoring program included:

- tracking the overall changes in schizophrenia exacerbation symptoms accompanied by manifestations of depression using the Clinical Global Impression Severity (CGI-S) and Clinical Global Impression Improvement (CGI-I) scales [44];
- determining the changes (reduction) in depressive disorders on the CDSS scale [45, 46];
- determining the changes in negative symptoms using the five-item NSA-5 scale [47];
- studying the changes in the subjective assessment of cognitive impairment using the PDQ-20 questionnaire [48]; and
- conducting a dynamic assessment of social functioning using the PSP scale [47, 50–52].

METHODS

Study design

Observational cohort prospective study of the changes in schizophrenia exacerbations occurring with a combination of psychotic and depressive symptoms.

Clinical study conditions

The study was conducted at state budgetary institutions in Moscow: Mental-health Clinic No. 1 named after N. A. Alexeev and Mental-health Clinic No. 4 named after P. B. Gannushkin. In the study, the sample included men and women with a confirmed diagnosis of paranoid schizophrenia who had completed the exacerbation relief therapy and displayed depressive symptoms during early remission (stabilization) and who, in the opinion of their attending physicians, had indications for treatment with a combination of one of the SGAs (quetiapine, olanzapine, risperidone, or paliperidone) and the AD vortioxetine,

all prescribed at the recommended doses. The attending physician chose a treatment regimen for each patient in real clinical practice based on the interests of the patient, therapeutic indications, and safety.

The conduct of this study and data collection included a total observation period for patients with schizophrenia and comorbid depressive disorders from December 3, 2020, to September 1, 2022.

All the patients whose mental state and social functioning were monitored received full information about the study and gave written consent to participate in it. The study protocol, patient information, and informed consent form, as well as the case report form, were reviewed, and the study was approved at a meeting of the Ethics Committee of Mental-health Clinic No. 1 named after N. A. Alexeev (Minutes of meeting No. 3 dated November 19, 2020).

Study participants

Inclusion criteria for the observational study:

- written informed consent of the patient to the collection of his/her socio-demographic and medical data and answers to the questions in psychometric scales, as well as to the processing of anonymized personal socio-demographic and medical data;
- age of the patient from 18 to 60 years (inclusive);
- paranoid schizophrenia (F20) diagnosed according to the ICD-10, including (F20.00 continuous; F20.01 episodic with a progressive defect; F20.02 episodic with a stable defect; F20.03 episodic relapsing (recurrent); F20.09 observation period of less than a year);
- the patient suffered schizophrenia exacerbation, which caused a change in the organizational form of the psychiatric care (treatment in a psychiatric hospital or day hospital), completed the relief therapy stage no more than a week prior and continues treatment in a day hospital, or has just started outpatient treatment aimed at stabilizing the disease;
- during early remission (stabilization), the patient retains symptoms of depression that cannot be eliminated by SGA monotherapy, and, therefore, the physician made the decision to prescribe a combination of SGA and the AD vortioxetine;
- quite effective, according to the physician, therapy of psychotic symptoms with one of the common SGAs (quetiapine, olanzapine, risperidone or paliperidone) that should be continued in future pursuant to clinical indications; and
- prescription of vortioxetine as an adjuvant treatment for depression by the attending physician (the physician's decision to use this drug was not determined by the program design and was made regardless of the goals of this study).

Non-inclusion criteria:

- refusal of patients to participate in the observation and examination using the psychometric scales;
- participation of patients in any other clinical or observational study of the effectiveness of medicinal products;
- contraindications to vortioxetine, which were determined by the attending physician on the basis of the clinical picture of the disease, existing concomitant diseases, and other individual risks, as well as contraindications specified in the instructions for the use of vortioxetine approved by the Ministry of Health of the Russian Federation;
- clinically significant medical diseases of the kidneys, liver, cardiovascular system, respiratory system, cerebrovascular disorders in the decompensation stage, oncological and other progressive diseases;
- a history of epilepsy or convulsive states;
- a history of severe drug allergy or hypersensitivity to vortioxetine or its ingredients; and
- dependence on a psychoactive substance (diagnosis or clinical manifestations within 6 months prior to inclusion in the study).

The patient was excluded from the program in the following cases:

- withdrawn informed consent, refusal to take medications prescribed within the program, or refusal to follow the procedures of the observational program;
- failure to take vortioxetine or an antipsychotic for 5 consecutive days;
- the need to stop one of the prescribed drugs (vortioxetine or antipsychotics) due to side effects or the risk of deterioration of the medical condition; the need to stop one of the prescribed drugs (vortioxetine or antipsychotics) due to a deterioration of the mental state;
- if, according to the physician, there was a need to change the treatment regimen, for example, changing the antipsychotic, prescribing a second antipsychotic

with a pronounced selective antipsychotic effect, the apparent needed to prescribe another AD;
- any other situations where discontinuation, change of therapy or the decision to terminate observation was made by the attending physician or the patient in the interests of the latter; or
- other circumstances interfering with proper treatment and monitoring of the patient.

All patients received SGA and vortioxetine therapy based on clinical need and in accordance with the Russian Clinical Guidelines for the Treatment of Schizophrenia and Depressive Disorders. The treatment regimen for SGA and vortioxetine suggested the possibility of single or double oral administration of the drug at doses permitted by clinical guidelines and the approved instructions for the drugs. Since the observed patients had individually pronounced symptoms, course, and history of schizophrenia, concomitant therapy was allowed (mood stabilizers, tranquilizers and other drugs with a predominantly sedative effect, correctors of adverse neurological symptoms), which was prescribed by the attending physician according to indications: due to existing affective fluctuations, anxiety or the side effects of the psychopharmacotherapy. Treatment with SGA, vortioxetine, and other concomitant drugs, their prescription, discontinuation, selection, and dose modification were determined by the therapeutic indications of these drugs and the doses recommended in the instructions, clinical need, and the interests of patients, but not the goals of the study.

The patients whose mental state changes were monitored formed five observation groups:

1) Receiving combination treatment with quetiapine and vortioxetine;
2) Receiving combination treatment with olanzapine and vortioxetine;
3) Receiving combination treatment with risperidone and vortioxetine;
4) Receiving combination treatment with paliperidone and vortioxetine; and
5) Receiving monotherapy with one of the SGAs (quetiapine, olanzapine, risperidone or paliperidone) without AD.

The program is planned to include 250 patients. To date, the analysis has included 160 patients who have completed the observation program or have withdrawn from the observation for various reasons.

A qualitative determination of psychopathological manifestations and an ordinal assessment of the severity of symptoms were carried out at baseline (before the start of treatment, on Day 1, Visit 1) and then on Day 90 (Visit 2) and Day 180 (Visit 3) of outpatient treatment with an acceptable interval of ± 10 days. Thus, the maximum duration of the observation period for each patient was 180 days (25 weeks or 6 months).

Assessment tools

The main method of data collection was the clinical and descriptive method, which included the study of the medical history, clarification of patient complaints, monitoring of the changes in their mental and physical state, and clarification of the peculiarities of their social functioning. A case report form was developed for the study, which included depersonalized data on age, diagnosis, concomitant therapy, the presence or absence of adverse effects of therapy, and the predominant symptoms and their severity. The time between the beginning and end of the study was recorded, indicating the reasons for the latter. Ordinal scales were used to quantify the changes in psychotic, depressive, negative symptoms, and the quality of social functioning at all visits:

1) The CDSS scale [45, 46] consisting of 9 items, each rated on a scale of 0 to 3. The scale showed high internal and inter-rating reliability in assessing depressive states in schizophrenia. [46];
2) The CGI-S and CGI-I scales, which allow for the most general assessment of the severity of a mental disorder based on the clinical impression of the physician [44, 53, 54];
3) The NSA-5 scale consisting of 5 items, each rated on a scale of 0 to 4. The scale was developed and tested for validity and reliability in determining the severity of negative symptoms in patients with schizophrenia [47];
4) The PDQ-20 questionnaire, consisting of 20 items, each rated on a scale of 0 to 4, and the scale result being the sum of the scores of all 20 items. The questionnaire showed its effectiveness in studying the subjective experience of deficiencies in cognitive functioning by patients during remission of schizophrenia [48]; and
5) The PSP scale, developed as a result of integrating the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) and the Global Assessment Functioning (GAF) scale. PSP is a scale with a maximum

score of one hundred, which is divided into 10 equal intervals with an ordinal designation [49]. The assessment takes into account four categories of functioning: potentially rewarding activities, relationships with loved ones and other social relationships, self-care, and harassing and aggressive behavior. The scale has proven to be a reliable and fast way to measure personal and social functioning, with a number of advantages over other tools [49, 50–52, 55].

The main indicator of effectiveness in the observational program was a significant increase in the average final score on the PSP scale and an increase in its final score of at least 10.7 (17.1%), which is consistent with the calculated Minimum Detectable Change (MDC) [52]. Secondary efficacy endpoints were a decrease in the manifestations of depression expressed as a decrease of at least 1.3 points on the CDSS scale, which is consistent with the calculated Minimum Clinically Important Difference (MCID) [45], a significant decrease in the mean CGI-S score and mean PDQ-2 total score.

Statistical analysis

Given that the general group of patients taking combination therapy with SGA + vortioxetine and SGA monotherapy had significant differences in the distribution of the leading syndrome, a 1 : 1 case-control match was created according to the criteria for complete matching by sex and the leading syndrome and an age limit of 2 years. The final sample of the study consisted of patients from both groups who met the criteria for the case-control search. The primary endpoint was the treatment-induced change in the total score on depression, assessed on the CDSS scale, and secondary endpoints were the total scores on the PDQ-20, NSA-5, and PSP scales, reflecting the severity of negative disorders assessed by the clinician and the patient and overall functioning, respectively. The time to early withdrawal from the study in both groups was studied as an exploratory endpoint.

The general characteristics of the population are presented by the methods of descriptive statistics with the presentation of continuous data in the form of mean and standard deviations (SD) of medians and first and third quartiles (Q1 and Q3). Categorical data are presented as absolute and relative frequencies. Comparison of the baseline parameters of the representation of various clinical variants of schizophrenia and psychopathological syndromes in independent samples was carried out using Pearson's χ^2 test.

The primary and secondary endpoints were examined in a separate repeated measures ANOVA model with a fixed group factor assessing between-group contrasts by the changes in the respective scores between Visit 1 and Visits 2 and 3.

The last observation carried forward (LOCF) approach was used to fill in the missing values. Differences in early withdrawal times were analyzed using the Kaplan-Meier survival curve analysis comparing the differences between groups using the log-rank test, calculating the mean duration of study participation for each group, and the relative risk score for full study completion.

All analyses were performed using the GraphPad software (GraphPad Prism version 9.3.1 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com), except for the survival analysis, which was performed using the NCSS software (NCSS 2021 Statistical Software (2021)). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss).

The analysis included all patients who had completed observation by September 1, 2022, including those who withdrew from the study early. The LOCF approach was used for patients who withdrew from the study early.

RESULTS

Participant characteristics

The analysis included 160 patients (Table 1) who completed the observation program or withdrew from the observation for various reasons.

Descriptive statistics for the total sample are shown in Table 2. The total sample consisted of 110 patients who received SGA + vortioxetine and 50 patients who received SGA alone.

All patients participating in the observational program were diagnosed with paranoid schizophrenia with various course variants (Table 2). The mean age in the entire sample and in patients of different sexes did not have significant differences. There were no differences in the level of education or employment rates. There were more cases with schizophrenia characterized by an episodic course with a progressive defect in the general sample of patients included in the general observational arm with combination therapy (SGA + vortioxetine), while the control group (SGA monotherapy), on the contrary, included more cases with recurrent schizophrenia (p <0.001).

Table 1. Number of study patients by drug therapy regimen

No.	Compared groups of patients receiving different therapy options	Target number of patients	Number of patients included in the analysis (who completed or withdrew from the study by November 1, 2022)	Number of patients included in the case-control analysis
1.	Combination treatment with one of the SGAs and vortioxetine	200	110	39
1.1.	Combination treatment with quetiapine and vortioxetine	50	32	10
1.2.	Combination treatment with olanzapine and vortioxetine	50	28	9
1.3.	Combination treatment with risperidone and vortioxetine	50	17	12
1.4.	Combination treatment with paliperidone and vortioxetine	50	33	8
2.	Monotherapy with one of the SGAs (quetiapine, olanzapine, risperidone or paliperidone) without AD	60	50	39
	Total number of patients	250	160	78

Table 2. Descriptive data from the total sample of patients receiving combination therapy with SGA + vortioxetine and SGA monotherapy

	Vortioxetine ***n=110***	**Control** ***n=50***	**[ALL]** ***n=160***	***p*-value**
Age[1]	34.0 (26.2; 44.0)	36.0 (31.2; 42.8)	34.0 (27.8; 44.0)	U=2455, *p*=0.277
Gender[2]:				**χ^2 =0.357, df=1, *p*=0.550**
Female	56 (50.9%)	28 (56.0%)	84 (52.5%)	
Male	54 (49.1%)	22 (44.0%)	76 (47.5%)	
Education[2]:				**χ^2=7.322, df=3, *p*=0.062**
Incomplete secondary education	7 (6.36%)	0 (0.00%)	7 (4.38%)	
Secondary education	39 (35.5%)	11 (22.0%)	50 (31.2%)	
Specialized secondary education	26 (23.6%)	15 (30.0%)	41 (25.6%)	
Postgraduate	38 (34.5%)	24 (48.0%)	62 (38.8%)	
Occupation[2]:				**χ^2=4.355, df=3, *p*=0.226**
Employed	26 (23.6%)	19 (38.0%)	45 (28.1%)	
Student	6 (5.45%)	3 (6.00%)	9 (5.62%)	
Student and employed	2 (1.82%)	0 (0.00%)	2 (1.25%)	
Unemployed	76 (69.1%)	28 (56.0%)	104 (65.0%)	
Living with[2]:				**χ^2=1.346, df=1, *p*=0.246**
Alone	16 (14.5%)	4 (8.00%)	20 (12.5%)	
With relatives	94 (85.5%)	46 (92.0%)	140 (87.5%)	
Diagnosis[2]:				**χ^2 =17.576, df=3, *p* <0.001**
F20.00	19 (17.4%)	6 (12.0%)	25 (15.7%)	
F20.01	72 (66.1%)	20 (40.0%)	92 (57.9%)	
F20.03	13 (11.9%)	18 (36.0%)	31 (19.5%)	
F20.09	5 (4.59%)	6 (12.0%)	11 (6.92%)	

Table 2. Descriptive data from the total sample of patients receiving combination therapy with SGA + vortioxetine and SGA monotherapy

	Vortioxetine ***n=110***	**Control** ***n=50***	**[ALL]** ***n=160***	***p*-value**
Leading syndrome[2]:				**χ^2 =18.729, df=5, *p*=0.002**
Affective-delusional	17 (15.5%)	20 (40.0%)	37 (23.1%)	
Apathic-abulic	15 (13.6%)	4 (8.00%)	19 (11.9%)	
Depressive	36 (32.7%)	6 (12.0%)	42 (26.2%)	
Hallucinatory-paranoid	22 (20.0%)	15 (30.0%)	37 (23.1%)	
Neurosis-like	9 (8.18%)	3 (6.00%)	12 (7.50%)	
Psychopatic-like	11 (10.0%)	2 (4.00%)	13 (8.12%)	
Disease duration[1]	7.00 [3.00; 15.0]	8.00 [4.00; 14.0]	8.00 [4.00;15.0]	U=2701, *p*=0,858
Number of hospitalizations[1]	3.00 [1.00; 5.00]	2.00 [1.25; 5.00]	2.00 [1.00;5.00]	U=2688, *p*=0.816
Disability grade[2,*]:				**χ^2=1.625, df=3, *p*=0.654**
No disability	42 (38.2%)	23 (46.0%)	65 (40.6%)	
The first group of disability	1 (0.91%)	0 (0.00%)	1 (0.62%)	
The second group of disability	58 (52.7%)	22 (44.0%)	80 (50.0%)	
The third group of disability	9 (8.18%)	5 (10.0%)	14 (8.75%)	
Antipsychotic[2]:				**χ^2=1.321, df=3, *p*=0.724**
Olanzapine	32 (29.1%)	17 (34.0%)	49 (30.6%)	
Paliperidone	17 (15.5%)	7 (14.0%)	24 (15.0%)	
Quetiapine	33 (30.0%)	17 (34.0%)	50 (31.2%)	
Risperidone	28 (25.5%)	9 (18.0%)	37 (23.1%)	

Note: [1] Median (1st and 3rd quartile), Mann–Whitney U-test; [2] Frequency (Percentage), Pearson χ^2-test. (*) — the first group is the heaviest, the third is the lightest.

Significant differences were also found in in relation to what syndrome was detected at the time of inclusion of patients in the study: the general sample of combination therapy included more patients with a predominance of depression, while the control group included more patients with an affective-delusional syndrome (*p*=0.002).

Case-control matching was conducted for sex (full match), leading syndrome (full match), and age (2 years tolerance) to obtain comparable groups. As a result, in each compared cohort (the cohort receiving combination therapy with SGA with the addition of vortioxetine and the cohort receiving SGA monotherapy), 39 cases were selected with established syndromes reflected in the medical documentation: affective-delusional syndrome in 15 (38.5%) cases, hallucinatory-paranoid syndrome in 13 cases (33.3%), depressive syndrome in 6 cases (14.4%), apathetic-abulic syndrome in 3 cases (7.7%), neurosis-like syndrome in 1 cases (2.6%), and psychopathic syndrome in 1 case (2.6%) in each group. Thus, the two cohorts did not differ in terms of predominant psychopathological symptoms and dominant syndrome (*p*=1.0). Their detailed characteristics are presented in Table 3. Significant differences in the established diagnostic codes remained between the groups; however, all diagnoses were within the F20.0 section and differed only in the course type, but not in the leading syndrome. In all other parameters, both groups were comparable. All subsequent analyses of observed changes in depression scores in patients with schizophrenia treated with SGA + vortioxetine and SGA monotherapy were performed in equivalent case-control groups. At the interim analysis stage, due to the small number of patients who had received each specific SGA, the comparison of the effectiveness of their combinations with vortioxetine and monotherapy did not yield reliable data.

Table 3. Descriptive data from the groups of patients receiving combination therapy with SGA + vortioxetine and SGA monotherapy formed by case-control matching

	Vortioxetine *n*=39	**Control *n*=39**	**[ALL] *n*=78**	**p-value**
Age[1]	35.0 (30.5;39.0)	36.0 (31.0; 40.0)	35.5 (31.0; 40.0)	U=726.5, *p*=0.734
Gender[2]:				**χ^2=0.0, df=1, *p*=1.0**
Female	23 (59.0%)	23 (59.0%)	46 (59.0%)	
Male	16 (41.0%)	16 (41.0%)	32 (41.0%)	
Education[2]:				**χ^2=8.70, df=3, *p*=0.03**
Incomplete secondary education	3 (7.69%)	0 (0.00%)	3 (3.85%)	
Secondary education	17 (43.6%)	9 (23.1%)	26 (33.3%)	
Specialized secondary education	7 (17.9%)	15 (38.5%)	22 (28.2%)	
Postgraduate	12 (30.8%)	15 (38.5%)	27 (34.6%)	
Occupation[2]:				**χ^2=3.73, df=3, *p*=0.29**
Employed	10 (25.6%)	16 (41.0%)	26 (33.3%)	
Learning	2 (5.13%)	2 (5.13%)	4 (5.13%)	
Learning and employed	2 (5.13%)	0 (0.00%)	2 (2.56%)	
Unemployed	25 (64.1%)	21 (53.8%)	46 (59.0%)	
Living with[2]:				**χ^2=3.14, df=1, *p*=0.08**
Alone	7 (17.9%)	2 (5.13%)	9 (11.5%)	
With relatives	32 (82.1%)	37 (94.9%)	69 (88.5%)	
Diagnosis[2]:				**χ^2=11.73, df=3, *p*=0.008**
F20.00	4 (10.3%)	3 (7.69%)	7 (8.97%)	
F20.01	29 (74.4%)	16 (41.0%)	45 (57.7%)	
F20.03	5 (12.8%)	14 (35.9%)	19 (24.4%)	
F20.09	1 (2.56%)	6 (15.4%)	7 (8.97%)	
Leading syndrome[2]:				**χ^2=0.0, df=5, *p*=1.0**
Affective-delusional	15 (38.5%)	15 (38.5%)	30 (38.5%)	
Apathic-abulic	3 (7.69%)	3 (7.69%)	6 (7.69%)	
Depressive	6 (15.4%)	6 (15.4%)	12 (15.4%)	
Hallucinatory-paranoid	13 (33.3%)	13 (33.3%)	26 (33.3%)	
Neurosis-like	1 (2.56%)	1 (2.56%)	2 (2.56%)	
Psychopatic-like	1 (2.56%)	1 (2.56%)	2 (2.56%)	
Disease duration[1]	10.0 [4.50; 16.5]	8.00 [4.50; 13.5]	8.50 [4.25; 14.8]	U=690.5, *p*=0.484
Number of hospitalizations[1]	2.00 [1.00; 4.50]	2.00 [2.00; 5.00]	2.00 [1.00; 5.00]	U=695, *p*=0.503
Disability grade[2,*]:				**χ^2=1.43, df=2, *p*=0.49**
No disability	14 (35.9%)	19 (48.7%)	33 (42.3%)	
The first group of disability	21 (53.8%)	16 (41.0%)	37 (47.4%)	
The second group of disability	4 (10.3%)	4 (10.3%)	8 (10.3%)	
The third group of disability				
Antipsychotic[1]:				**χ^2=4.34, df=3, *p*=0.227**
Olanzapine	9 (23.1%)	13 (33.3%)	22 (28.2%)	
Paliperidone	8 (20.5%)	7 (17.9%)	15 (19.2%)	
Quetiapine	10 (25.6%)	14 (35.9%)	24 (30.8%)	
Risperidone	12 (30.8%)	5 (12.8%)	17 (21.8%)	

Note: [1] Median (1st and 3rd quartile), Mann–Whitney U-test; [2] Frequency (Percentage), Pearson χ^2-test. (*) — the first group is the heaviest, the third is the lightest.

Changes in symptoms and social functioning parameters

ANOVA test results for repeated measures of the total score on the CDSS, NSA-5, and PDQ-20 scales and the final score on the PSP scale revealed a statistically significant effect of the interaction between the visit and group variables on the CDSS and PSP scales, as well as a statistically significant effect of the visit variable in relation to the total score for each of the scales (Table 4, Figure 1). Detailed statistics on the differences between the groups are presented in Table S1 (in the Supplementary). These results suggest that, regardless

Table 4. Two-way Repeated-measures ANOVA results in changes of CDSS, NSA-5, PDQ-20 and PSP total scores between SGA and SGA + vortioxetine study groups

	Source of variation	Sum of Squares	df	Mean Square	f	*p*	η^2_p
CDSS	Visit	1116.009	2	558.004	31.062	<0.001	0.29
	Visit × Group	143.859	2	71.930	4.896	0.009	0.065
	Residual	2730.547	152	17.964			
NSA-5	Visit	797.598	2	398.799	39.606	<0.001	0.343
	Visit × Group	37.872	2	18.936	1.881	0.156	0.024
	Residual	1530.53	152	10.069			
PQD-20	Visit	3578.88	2	1789.44	31.775	<0.001	0.295
	Visit × Group	328.368	2	164.184	2.915	0.057	0.037
	Residual	8560.085	152	56.316			
PSP	Visit	2206.778	2	1103.389	5.569	0.005	0.068
	Visit × Group	1451.444	2	725.722	3.663	0.028	0.046
	Residual	30115.778	152	198.13			

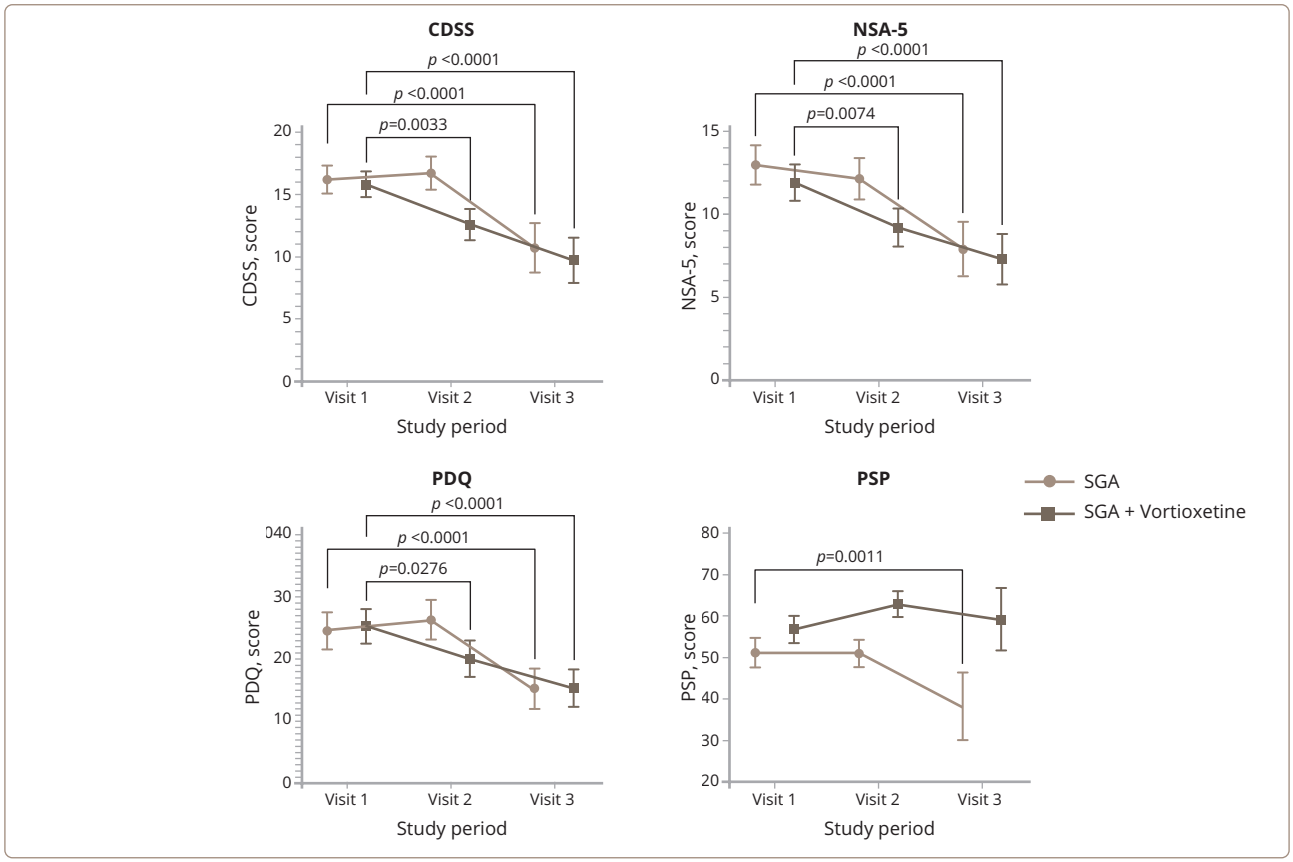

Figure 1. CDSS, NSA-5, PDQ-20 and PSP total scores across the study in SGA and SGA + vortioxetine groups.

of the therapeutic group, patients at the end of the observation period showed a significant decrease in the level of depression assessed based on the CDSS scale, as well as the severity of negative symptoms assessed by the clinician (NSA-5 scale), and cognitive symptoms based on subjective assessment (PDQ-20 scale), as well as an improvement in personal and social functioning (increased final score on the PSP scale). The size of the η^2p effect for the visit factor in all scales measuring clinical parameters turned out to be higher than that for the interaction of the visit and group factors. In other words, as a result, depressive and negative symptoms, cognitive impairment, and the level of social functioning tended to improve after six months of early remission regardless of whether the combination therapy or monotherapy was used.

There were also significant differences between the compared main (SGA + vortioxetine) and control (SGA) groups in terms of the changes in the total score on the CDSS and PSP scales, which is presented in Table 5. Thus, the mean CDSS score decreased significantly from 15.749 (95% CI: 14.733–16.765) to 12.501 (11.28–13.722) at Visit 2 and to 9.649 (7.854–11.445) at Visit 3 (all p <0.01) in the SGA + vortioxetine group, and it increased from 16.12 (15.02–17.219) to 16.645 (15.324–17.966) at Visit 2 and decreased significantly to 10.642 (8.699–12.585) at Visit 3 (p <0.001) in the SGA group. Figure 1 shows an interesting aspect of the changes in the clinical scores: a noticeable improvement in the SGA + vortioxetine group by Visit 2 in the absence of a similar improvement in the control group, and the achievement of approximately the same scores in both groups by Visit 3. In particular, the mean CDSS score at Visit 2 in the SGA + vortioxetine group was significantly lower than that in the SGA group (p <0.001, Table 5). Parameters η^2_p=0.235 for intergroup differences of the changes in the total CDSS score at Visit 2 indicate a large contribution of vortioxetine to the changes in depressive symptoms for this period. There were also significant differences at Visit 2 in the total NSA-5 score (p=0.003) at η^2_p=0.121, that is, with a moderate contribution of vortioxetine to the changes in negative symptoms, as well as differences in the total PDQ score (p=0.046) at η^2_p=0.212, which indicates a large contribution of vortioxetine to the changes in the subjective assessment of cognitive function.

By Visit 3, the differences in the scores for the severity of depressive, negative symptoms, and cognitive impairment smoothed out. The small effect size (η^2_p) of vortioxetine in the score differences at Visit 3 indicate the influence of other factors not related to the action of adjuvant AD (Table 5).

This observation shows multidirectional changes of social functioning in the compared groups, assessed based on the total PSP score. The mean PSP score in the SGA + vortioxetine group increased not significantly compared to Visit 1; from 56.859 (53.628–60.09) to 59.338 (51.902–66.775). In the SGA control group, on the contrary, the mean final PSP score at Visit 2 remained almost

Table 5. CDSS, NSA-5, PDQ-20 and PSP total scores across the study in SGA and SGA + vortioxetine groups

Measure	Visit	SGA			Vortioxetine + SGA			Between-group contrast in comparison with visit 1 statistics		
		Mean	LCL 95%	UCL 95%	Mean	LCL 95%	UCL 95%	f	*p*-value	η^2p
CDSS	**1**	16.12	15.02	17.219	15.749	14.733	16.765	-	-	-
	2	16.645	15.324	17.966	12.501	11.28	13.722	21.535	< 0.001	0.235
	3	10.642	8.699	12.585	9.649	7.854	11.445	0.197	0.659	0.003
NSA5	**1**	12.984	11.819	14.15	11.919	10.842	12.996	-	-	-
	2	12.133	10.904	13.361	9.209	8.074	10.344	9.663	0.003	0.121
	3	7.905	6.283	9.527	7.308	5.81	8.807	0.159	0.692	0.002
PDQ	**1**	24.36	21.399	27.321	25.105	22.369	27.841	-	-	-
	2	26.139	23.017	29.261	19.901	17.016	22.786	18.839	< 0.001	0.212
	3	15.065	11.855	18.276	15.193	12.226	18.16	0.057	0.812	0.001
PSP	**1**	51.252	47.756	54.749	56.859	53.628	60.09	-	-	-
	2	51.042	47.773	54.311	62.929	59.909	65.95	8.833	0.004	0.112
	3	38.334	30.287	46.382	59.338	51.902	66.775	7.091	0.01	0.092

unchanged. But by the end of the observation period, it had decreased significantly, from 51.252 (47.756–54.749) to 38.334 (30.287–46.382) (p=0.0011). The PSP scores had significant intergroup differences at Visits 2 and 3 (p=0.004 and p=0.01, respectively), which shows the resulting significant effect of the combination therapy with SGA + vortioxetine on the level of social functioning of patients with schizophrenia with depressive symptoms that persist during early remission.

Study withdrawal analysis

Analysis of the time to early withdrawal from the study (Figure 2) showed that significantly more patients in the SGA + vortioxetine group completed the study program (n=27, 69.23%) compared with the SGA group (n=13, 33.33%) (χ^2 =14.618, df=1, p <0.001, log-rank test). The mean survival time in the SGA group was significantly less (p <0.001) and amounted to 101.436 436 days (95% CI: 81.518–121.354), and in the SGA + vortioxetine group it was 161.744 days (147.981–175.506). The relative likelihood of full study completion in the vortioxetine + SGA group compared with SGA was 3.618 (1.871–6.994).

Drug tolerability analysis

Sixty-two (62) adverse events (AEs) were reported in the SGA + vortioxetine group, and 67 AEs were reported in the SGA group. A complete list of AEs is presented in Table S2 in the Supplementary. Among the AEs reported in the SGA + vortioxetine group, 11 occurred in 5% of patients, drowsiness in 6 (15.4%), tremor in 5 (12.8%), akathisia in 5 (12.8%), impaired attention in 5 (12.8%), weight gain in 5 (12.8%), nausea in 5 (12.8%), dizziness in 4 (10.3%), anxiety in 4 (10.3%), weakness in 3 (7.8%), irritability in 3 (7.8%), and pruritus in 3 (7.8%). The remaining AEs were reported in isolated cases. These 11 AEs were also reported in more than 5% of the SGA group: worsening depression in 10 patients (25.6%), drowsiness in 6 (15.4%), tremor in 6 (15.4%), weight gain in 6 (15.4%), anxiety in 6 (15.4%), akathisia in 5 (12.8%), impaired attention in 5 (12.8%), weakness in 4 (10.3%), tachycardia in 3 (7.8%), and hyperprolactinemia in 3 (7.8%). In the absence of significant differences due to the sample size, it is interesting that nausea and pruritus were more common in the SGA + vortioxetine group, as these AEs are quite typical for vortioxetine. An increase in depression

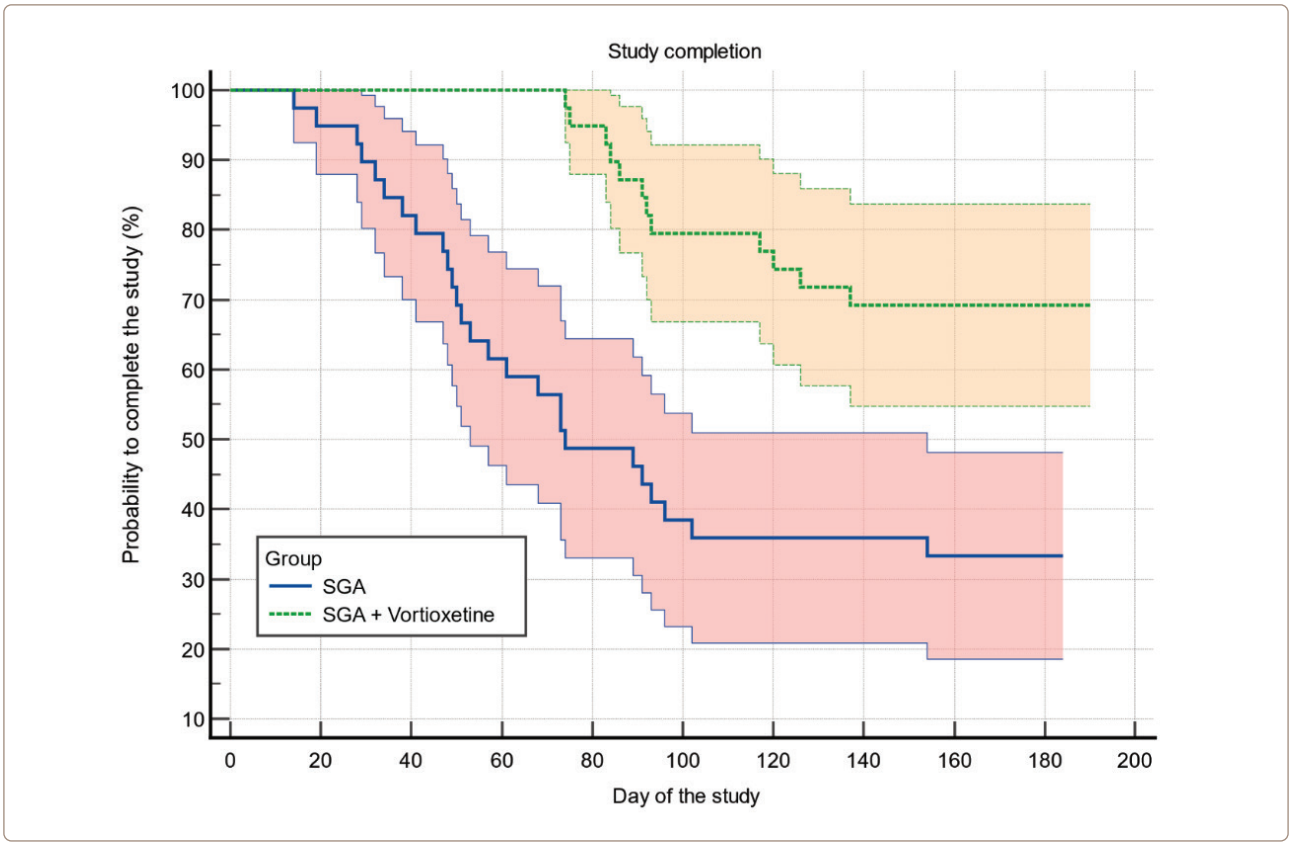

Figure 2. Kaplan-Meier curves of the probability to complete the study for patients from the SGA and SGA + vortioxetine groups.

was the most common and an exacerbation of psychotic symptoms was somewhat more common in the control group. In general, the composition of AE was similar and quite typical for the main basic antipsychotic therapy: in both groups, the most common were mild extrapyramidal symptoms (EPS), as well as drowsiness, weight gain, and impaired concentration.

DISCUSSION

We report here the results of Russia's first observational study of the psychosocial functioning of schizophrenic patients with depressive symptoms during early remission receiving combination therapy with vortioxetine and second-generation antipsychotics. This study showed that a 6-month course of treatment with a combination of SGA and vortioxetine prescribed according to clinical need at flexible doses provides significant improvement in the PSP final score (primary endpoint), CDSS total score (key secondary endpoint), and other secondary endpoints (CGI-S score and NSA-5 score). The results of this study confirm that the addition of vortioxetine to basic therapy with a second-generation antipsychotic is an effective and well-tolerated treatment option for schizophrenia with concomitant depressive symptoms during early remission. The 6-month prospective observational study of the changes in depressive symptoms and social functioning of patients during early remission of paranoid schizophrenia for patients receiving combination therapy with SGA and vortioxetine and SGA monotherapy after case-control matching showed a significant and clinically relevant improvement in depressive, negative symptoms, self-assessment of cognitive abilities, and especially pronounced improvement in the quality of personal and social functioning.

A comparative analysis of the changes in clinical scale scores shows that the addition of vortioxetine to SGA therapy accelerates the reduction in the acuity of the symptoms of depression that persist or occur during regression of psychosis and early remission. The antidepressant effect in patients with schizophrenia is consistent with the available data on the efficacy of vortioxetine in the treatment of major depressive disorders [32, 35, 38, 40].

Moreover, the addition of vortioxetine to baseline SGA therapy contributes to an accelerated reduction in negative symptoms, regardless of how they are viewed, whether they are "transient" negative disorders that are inherent to a relapse and persist longer than positive symptoms, or depression-related negative symptoms; for example, "negative affectivity" [56] or negative symptoms due to developmental mechanisms common to depression, or an error inherent in the scale, when depressive symptoms fall under the assessment of the negative symptoms scale.

The study of patients' subjective assessment of their cognitive abilities showed that treatment with a combination of SGA + vortioxetine leads to a consistent and significant improvement in the average PDQ score, with a significant contribution of vortioxetine to its changes, while SGA monotherapy achieves improvement only after six months.

Vortioxetine adjunction has the greatest effect on the level of psychosocial functioning: by the second visit in the main group, the final PSP score had increased significantly and was significantly different from the control; this difference also persisted subsequently. The pronounced improvement in psychosocial functioning in the SGA + vortioxetine group coincides with a distinct antidepressant effect, a decrease in negative symptoms, and an increase in the self-assessment of cognitive abilities.

The fact that by the third visit, the differences in the scores assessing the severity of depressive, negative symptoms, and cognitive impairment had smoothed out can be explained by three circumstances: 1) spontaneous reduction in depressive symptoms as remission develops in a significant proportion of patients receiving any therapy regimens; 2) relatively delayed onset of the antidepressant effect of some SGAs; and, finally, 3) the achievement of the greatest possible improvement in the mental state and/or scores approaching the minimum possible values, when the probability of differences decreases.

A combination therapy with SGA and vortioxetine is characterized by a high rate of continuation of treatment (using statistical terminology, on-treatment survival) that is twice as high as that with SGA monotherapy: after a month and a half, the difference in the number of patients participating in the main and control groups reached statistical significance and persisted until the end of the observation period.

The addition of vortioxetine showed not only the effectiveness, but also the safety of this combination: patients do not experience the increase in the frequency

or severity of AEs typical for SGA. AEs typical for the combination regimen of SGA + vortioxetine were pruritus and nausea. In contrast, the use of vortioxetine reduced the risk of worsening depression, which is often observed in cases of SGA monotherapy. The good safety profile of vortioxetine is consistent with RCS data [32, 34].

Limitations of the study

Distinguishing between the negative symptoms of schizophrenia and the actual symptoms of depression, especially manifestations of the so-called "negative affectivity", remains difficult. Accepted diagnostic criteria and existing clinical scales do not solve this problem. Therefore, throughout the study, there was a risk of including heterogeneous cases with different psychopathological structures of depression itself and affective-delusional attacks, and an unequal relationship between delusional and depressive manifestations.

The study was observational and as close as possible to real clinical practice; it was not blind and did not use randomization. The observational design of the study led to selectivity of inclusion in different branches of observation: the control group, where patients received SGA monotherapy, included mainly patients with a relatively uniform regression of depressive-delusional attacks of schizophrenia and a lesser severity of depression, while patients with schizophrenia were much more likely to be in the main group where symptoms of depression were the primary manifestations during early remission. This is probably due to the fact that psychiatrists in real clinical practice, seeing a favorable regression of the affective-delusional (depressive-delusional) syndrome with a simultaneous reduction in its psychotic and depressive components, most often continued SGA monotherapy. On the contrary, when depressive manifestations persisted or increased in patients despite the reduction in psychotic symptoms, physicians usually diagnosed depressive syndrome instead of delusional and affective-delusional syndromes and vortioxetine was more often prescribed in addition to SGA. Such selectivity in the choice of treatment, explained by the physician's desire to reduce the patient's suffering and avoid the risks associated with insufficient therapy for depression, in our opinion, caused the significant differences in the distribution of the leading syndrome between the main sample of SGA + vortioxetine and the control group of SGA monotherapy. To level out this effect, a departure from the cohort study was made at the stage of intermediate analysis of the obtained data and case-control matching was used on the obtained material. This method allowed for a comparison in a clinically (syndromic) homogeneous sample, but also reduced the chances of identifying and, all the more so, proving more reliable differences.

CONCLUSION

In a 6-month observational study of the changes in the psychosocial functioning of schizophrenic patients with symptoms of depression during early remission receiving combination therapy with vortioxetine and second-generation antipsychotics in real clinical practice, the addition of vortioxetine to the basic therapy with SGA showed significant and clinically relevant improvement in depressive symptoms, negative symptoms, and the quality of social functioning. Combination therapy with vortioxetine and SGA, including quetiapine, olanzapine, paliperidone or risperidone, was well tolerated, and the main side effects of the treatment were weight gain, EPS, and sedative effects; these AEs are inherent to antipsychotics, and their frequency in combination therapy does not exceed that with monotherapy.

Article history:
Submitted: 14.02.2023
Accepted: 14.03.2023
Published Online: 24.03.2023

Authors' contribution:

Aleksandr Reznik designed the project and acted as the chief coordinator for the data collection from investigators; Aleksandr Mudrak, Nikolay Zakharov, Zhanna Popova, Anastasia Khoroshilova, Ilona Khurbatova, Alina Saifulina, Anton Eliseenko, Tatiana Matvievskaya, Angelina Khannanova collected the data; Timur Syunyakov analyzed the data; Aleksandr Reznik and Timur Syunyakov wrote the first draft of the manuscript, which has been revised by Aleksandr Reznik and upon input from the other co-authors.

Funding: This article was written without additional financial funding.

Conflict of interest: The authors declare no conflicts of interest.

Supplementary data

Supplementary material related to this article can be found in the online version at doi: 10.17816/CP3728

For citation:

Reznik AM, Syunyakov TS, Mudrak AV, Zakharov NB, Popova ZhB, Khoroshilova AN, Khurbatova IG, Saifulina AM, Eliseenko AM, Matvievskaya TK, Khannanova AN. Treatment of depression with vortioxetine and second generation antipsychotics during the period of remission formation in schizophrenia (interim data analysis). Consortium Psychiatricum. 2023;4(1):CP3728. doi: 10.17816/CP3728

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Efficacy of a Relaxation Scenario in Virtual Reality for the Comorbid Symptoms of Anxiety and Asthenia in a General Hospital Setting: A Pilot Comparative Randomized Open-Label Study

Эффективность применения релаксационного сценария в технологии виртуальной реальности в отношении коморбидных симптомов тревоги и астении в условиях соматического стационара: пилотное сравнительное рандомизированное открытое исследование

doi: 10.17816/CP221

Original research

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ABSTRACT

BACKGROUND: Patients in general hospitals often display concomitant signs of mental maladjustment: low mood, anxiety, apathy, asthenia, all of which can have a negative impact on the course of the underlying disease and the recovery process. One of the non-pharmacological approaches that has gained wider acceptance in medical practice in recent years is the use of procedures based on virtual reality.

AIM: Assess the efficacy of the new domestic, virtual reality application Flow as relates to symptoms of anxiety and asthenia in patients undergoing inpatient treatment.

METHODS: The study was open-label and had a comparison group; the patients were assigned to the experimental or control group using a randomization table. The patients were assessed using the Spielberger State Anxiety Inventory; the Fatigue Symptom Rating Scale; the Well-being, Activity, Mood questionnaire; the Depression Anxiety Stress Scale; and the Clinical Global Impression Scale. Physical parameters were measured before and after each virtual reality session. The obtained data were statistically processed.

RESULTS: The study involved 60 patients. In 40 patients, the treatment program included a course of five daily relaxation sessions in virtual reality; the control group consisted of 20 patients, who were treated in accordance with the usual practice of the institution. The addition of virtual reality sessions to the standard treatment course yielded significant advantage in terms of affective symptoms reduction in patients both after a single session and as a result of undergoing the full course, and several days after its completion. The patients in the experimental group also showed a significant decrease in blood pressure after the sessions, and this was most pronounced in individuals who initially had elevated and high blood pressure.

CONCLUSION: The use of relaxation program courses in the virtual reality application Flow is an effective and promising means of non-pharmacological care for non-psychiatric inpatients showing symptoms of anxiety, apathy, depressive mood, as well as hypertension.

АННОТАЦИЯ

ВВЕДЕНИЕ: Пациенты соматических стационаров нередко демонстрируют сопутствующие признаки психической дезадаптации — сниженное настроение, тревогу, апатию, астению, которые могут оказывать негативное влияние на течение основного заболевания и процессы восстановления. Одним из нелекарственных подходов, в последние годы все шире внедряемых в медицинскую практику, является использование методик на основе технологии виртуальной реальности.

ЦЕЛЬ: Оценить эффективность нового отечественного приложения виртуальной реальности Flow в отношении симптомов тревоги и астении у пациентов, проходящих стационарное лечение.

МЕТОДЫ: Исследование было открытым, с группой сравнения; определение пациента в экспериментальную либо контрольную группу происходило с использованием рандомизационной таблицы. Состояние пациентов оценивалось при помощи шкалы ситуативной тревожности Спилбергера, шкалы оценки симптома усталости, опросника «Самочувствие, активность, настроение», шкалы депрессии, тревоги, стресса и шкал общего клинического впечатления. До и после каждой сессии виртуальной реальности проводилось измерение физикальных показателей. Полученные данные обрабатывались статистически.

РЕЗУЛЬТАТЫ: В исследовании приняли участие 60 пациентов. У 40 пациентов в программу лечения был включен курс из пяти ежедневных релаксационных сессий в виртуальной реальности; контрольную группу составили 20 пациентов, которые проходили лечение в соответствии с рутинной практикой учреждения. Добавление к стандартному лечению курса сессий в виртуальной реальности создавало значимое преимущество в редукции у пациентов аффективных жалоб как после одного занятия, так и в результате прохождения курса и через несколько дней после его завершения. Пациенты экспериментальной группы также демонстрировали достоверное снижение показателей артериального давления после прохождения сессий, причем наиболее выраженным оно было у лиц с изначально повышенным и высоким давлением.

ЗАКЛЮЧЕНИЕ: Курсовое использование релаксационной программы в технологии виртуальной реальности Flow является эффективным и перспективным методом нелекарственной помощи пациентам соматического стационара в отношении жалоб на тревогу, апатию, снижение настроения, а также симптомов гипертонии.

Keywords: *virtual reality; non-pharmacological therapy; comorbid mental symptoms; maladjustment reaction; lowering blood pressure*

Ключевые слова: *виртуальная реальность; нефармакологическая терапия; коморбидные психические симптомы; реакция дезадаптации; снижение артериального давления*

INTRODUCTION

Physical illnesses are often accompanied by signs of stress and maladjustment, in the form of depressed mood and increased anxiety. It is reported that 18–33% of patients who have suffered a stroke also suffered from depression [1]; anxiety symptoms occur in 28% of non-psychiatric inpatients, and 8% meet the criteria for some anxiety disorder [2]. Affective symptoms and medical disorders have a compounding negative impact that manifests through psychological, behavioral, and physiological mechanisms. Anxiety and low mood may be a patient's reaction to disease, and a negative assessment of the prospects for recovery may limit that patient's usual activity and social circle; in turn, a physical illness can exacerbate the manifestations of an already existing mental disorder [3, 4]. Negative behavioral manifestations include addiction, sleep disorders, or violation of the treatment regimen [5]. Physiological mechanisms include increased inflammatory response and hypothalamic-pituitary-adrenal axis impairment [6]. Research also points to an association between anxiety disorders and hypertension [7]. Together, these factors can worsen the course and prognosis of the physical illness, reduce the effectiveness of treatment, and slow down recovery. Thus, the search for effective means of treatment of negative mental state is an important independent undertaking in the management of patients with physical illnesses.

The use of pharmacological resources for the treatment of comorbid symptoms of maladjustment, along with proven efficacy, has a number of limitations, such as an adverse increase in the pharmacological load; an often long period of effective dose selection; possible contraindications and side effects; and, for some drugs, the potential for addiction [8]. Non-pharmacological methods of treatment with comparable efficacy in such a context will have an advantage. Another traditional, and effective, form of care for various types of distress and maladjustment is psychotherapy. At the same time, data have been accumulating on the positive impact of different activities, such as meditation, yoga, various breathing practices, and mindfulness practices on the mental state [9, 10]. Literature suggests that meditation practices reduce stress levels and hypertension [11–13]. Studies also show that the regular use of meditation, relaxation, and breathing practices contributes to many positive changes in both the emotional state of those practicing them and aspects of their physical health, such as a significant reduction in stress hormones [14] and markers of chronic inflammation [15], as well as normalization of elevated blood pressure (BP) [16–19].

In an attempt to achieve a standardization and reproducibility of these types of care, investigators and professionals are increasingly turning to technologies that are based on virtual reality. Virtual reality (VR) is a simulated three-dimensional immersive environment in which the user can act according to prearranged scenarios [20]. In recent years, various VR applications have found increasingly wide application in medical practice, including programs for both specialists (training of specific skills, simulation of medical processes, etc.) and patients (relaxation and stress management, overcoming anxiety, neurorehabilitation, etc.) [21–23]. According to the results of these studies, VR-based applications show a level of efficacy comparable to that of pharmacological, and, sometimes, even superior efficacy as a treatment means for anxiety disorders [24], phobias [25], eating disorders [26], and other psychopathological conditions. Such data justify the attempts being made to transfer relaxation practices to high-tech platforms. VR technologies allow, on the one hand, to standardize the procedure, and, on the other hand, they do not rule out the possibility of customizing the scenario, taking the patient's condition into account, selecting the optimal program duration, setting breathing parameters, preferred locations, as well as other parameters.

In Russia, Viartech Development LLC has developed the Flow relaxation program, integrated into a capsule chair, for people with various manifestations of a stress reaction, anxiety, or tension.

The main goal of this study was to evaluate the efficacy of the relaxation scenario in the VR Flow technology in relation to the symptoms of anxiety and asthenia in patients undergoing inpatient treatment. Study hypothesis: taking a course of sessions of a specially designed relaxation VR scenario, in addition to the primary therapy, should help reduce the severity of anxiety and affective symptoms.

METHODS

Study design

The study used an open-label design with a comparison group and simple randomization.

Sample

The enrollment of study participants was carried out from March to June 2021 among patients of both sexes aged 18 to 68 years who were undergoing inpatient treatment at the Speech Pathology and Neurorehabilitation Center of the Moscow Healthcare Department.

The main inclusion criteria of the study were as follows:

— complaint of anxiety, bad mood, asthenia, tension, increased fatigue, and other manifestations of maladjustment;
— understanding of the study instructions and procedures, readiness and ability to sit through VR sessions, filling out of questionnaires and scales.

The exclusion criteria were as follows:

— severe cognitive, motor and/or speech impairments that prevent understanding of the instructions and limit one's ability to follow the study procedures;
— diagnosed epilepsy or a history of convulsive seizures;
— diagnosed mental illness (bipolar disorder, major depressive episode, schizophrenia, schizoaffective disorder, etc.);
— severe, decompensated or unstable physical illnesses.

Enrollment and randomization

The study information leaflet informed the patients that it was not known in advance to which group (experimental or control) they would be assigned, and that that would be determined randomly. All patients in the comparison group could, if they so desired, undergo a course of VR after completing the program.

The participants were assigned to a particular group as follows: After inclusion of a new patient and the signing of an informed consent form, the clinical researcher called authors of the protocol who had no relation to the recruitment of patients in the study and did not come into direct contact with them. A randomization table was used to assign patients to groups; according to this table, each participant's serial number was randomly assigned a code of one of two groups: 40 codes for the VR group and 20 codes for the comparison group. After the clinical researcher at the site had received the group code for a new participant, this information became open to everybody.

The enrollment continued until an equal ratio of male and female patients in each group was achieved; data from patients included at the end of the recruitment who did not meet the target 1 : 1 sex distribution were removed from the final analysis. In case of early withdrawal, the analysis included data collected at the time of exclusion. The primary ground for early withdrawal from the program was the end of hospitalization. The recruitment process is shown in Figure 1.

Evaluation tools

The following procedures were used to assess the condition of patients:

1. Spielberger State Anxiety Inventory [27]. This is a questionnaire to assess the severity of state anxiety (as opposed to anxiety as a personality trait), consisting of 20 statements that must be assessed on a 4-point scale. The procedure adaptation by Yu. L. Khanin provides the following indicative standards: 20–34 means a low level of anxiety, 35–44 means a moderate level of anxiety, and above 46 means a high level of anxiety.
2. The Daily Fatigue Impact Scale (D-FIS) [28], consisting of 8 statements, was developed to assess the current state and daily changes in the symptom of fatigue associated with non-psychiatric illnesses. The patient rates each statement on a 5-point scale (0–4); a higher symptom severity corresponds to a higher total score.
3. The Well-being, Activity, Mood (WAM) questionnaire [29] explores three aspects of the current psycho-emotional state indicated in the title. The subject is asked to correlate his current well-being with the scale assessment between pairs of words describing the poles of one state (for example, cheerful-gloomy, tense-relaxed). The result is separate scores on the subscales of well-being (WAM-W), activity (WAM-A), and mood (WAM-M); the 30–50 range is the average (normal) level for each of them.
4. The Depression, Anxiety and Stress Scale (DASS-21) [30] is a questionnaire consisting of 21 statements to be ranked on a 4-point scale (0–3) for an assessment of the states of depression, anxiety, and stress experienced by the subject during the preceding week. The scale is not diagnostic; the concepts of stress, anxiety, and depression were used by the developers as a continuum to describe subjective experience. The final assessment in this test is the total score: the higher it is, the more pronounced the negative affective symptoms of the state.

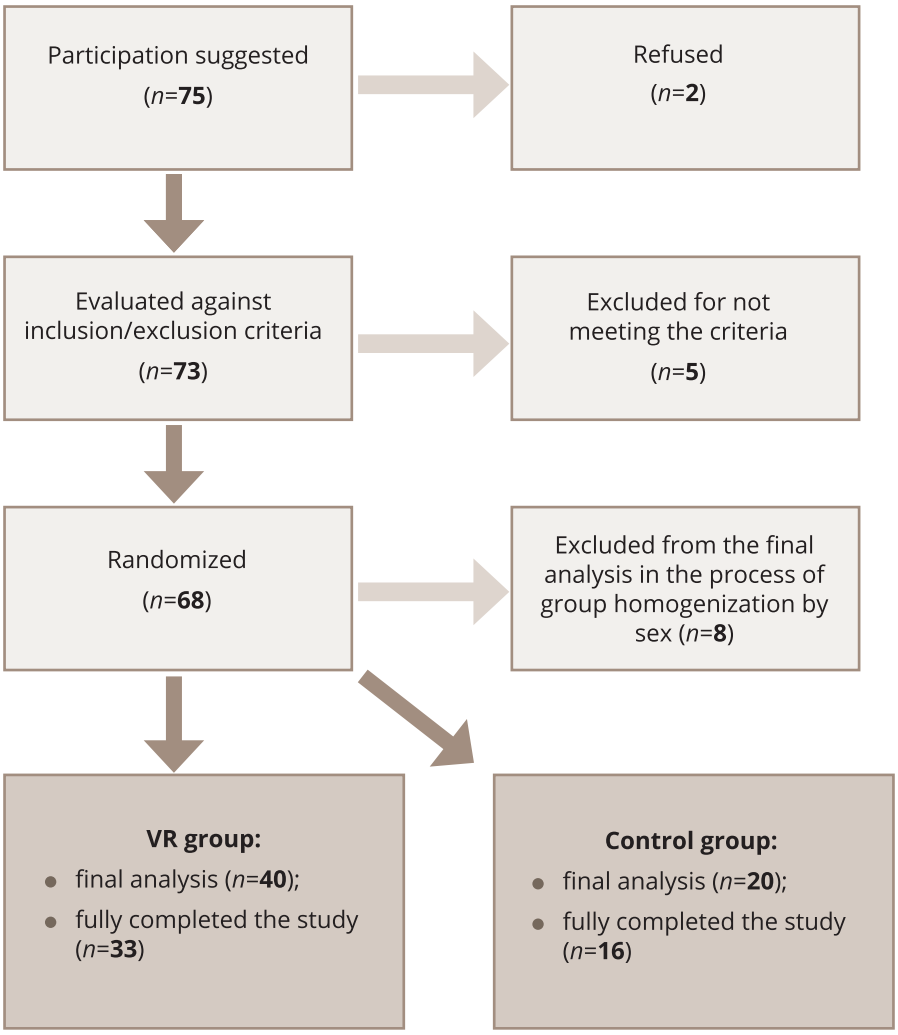

Figure 1. Participant flowchart.

All of these scales are self-questionnaires and are filled in by patients on their own.

Clinical Global Impression Scale-Severity (CGI-S) and Clinical Global Impression Scale-Improvement (CGI-I) [31] are filled in by the clinical researcher. These are 7-point scales in which the doctor is asked to assess the severity of the patient's condition as a whole (at the first visit) and the changes in the patient's condition (at subsequent visits) in comparison with other patients with a similar diagnosis based on their clinical experience.

Study procedures

Patients of the experimental group underwent a relaxation VR session on a daily basis for five days. Physical parameters (pulse rate) were measured before and after each session. Filling of the scales and questionnaires by the patient and patient's condition assessment by the investigator were performed twice on the first day of the study (before and after the VR session), after the final (fifth, if the patient had not dropped out earlier) session, and five days after the end of the course. The total duration of the program thus amounted to 10 days (+2–5 days).

Patients in the control group underwent the same procedures, excluding VR sessions. On the first day, the interval between the first and subsequent measurements was about 6 hours.

All patients received standard pharmacotherapy, in accordance with the established diagnosis.

The following are the main outcomes of the study: the psychometric characteristics of patients in the experimental and control groups at the first examination;

changes in the estimated parameters as a result of a single VR session, after a course of five sessions and long-term, as well as a comparison of these data with the results of the control group; assessment of the statistical significance of the changes in parameters for each of the groups; and data on changes in physiological parameters as a result of VR-relaxation.

Virtual reality scenario

All patients were given explanations about the upcoming VR sessions and their schedule by clinical researcher. To undergo the scenario, the patient was placed inside a specially equipped cocoon chair with a rotating bowl. Immediately before each relaxation session, the administrator of the VR capsule helped the participants to sit comfortably in the chair, fix the equipment (helmet, heart rate monitor), and provided support during the session.

The VR-program is a practice of guided relaxation, combining the methods of body therapy, hypnotherapy, work with negative emotional states and images. As part of the study, two virtual locations were used: a tropical beach and a mountainous landscape (Figure 2), which alternated uniformly for all participants in the study. The main characteristics that were taken into account when creating virtual locations were as follows: the practice space had to create a feeling of safety and comfort, be natural and at the same time cultivated, reflect the presence of the person in it, be filled and at the same time devoid of intense and stimulating elements that distract attention and interfere with focusing on internal processes. At the beginning and end of each session, the users assessed their state at the moment using a series of visual analog scales; they did this by placing a slider on these scales using the controller (joystick). The patients also noted the most pronounced emotions

Figure 2. Screenshots of Flow locations.

that they could detect in themselves at that moment. Depending on the assessments and responses of the patient, some stages of the practice were dynamically changed. Elements of scenario interactivity also included the ability to adjust some of the dynamic aspects of the scenario: the option to linger on one of the stages (for example, to better awareness of the ongoing processes), transition from one stage to the next.

One session took an average of 20 to 30 minutes, depending on the characteristics of the state indicated by the patient at the beginning of the scenario, and the preferred speed of navigation within it.

Description and technical characteristics of the equipment

The following devices were used: a capsule chair for working in VR; a PC-based VR Oculus Rift S headset with built-in tracking; NZXT H1 650W computer with Intel Core i5-10600kf processor; Polar OH1 heart rate tracker; Samsung Galaxy Tab A7 32GB LTE (SM-T505N); Huawei e3372 modem.

Statistical analysis

The obtained primary data were analyzed using the statistical software package Statistica 6.0, version for Windows (StatSoft Inc.).

Mean values (*M*) and standard deviation (*SD*) were used when processing the results. Deltas (the magnitude of changes in psychometric parameters compared to the baseline) were studied to compare the degree of psychological changes in the experimental and control groups. The significance of the differences between the groups at different stages of the study was assessed using the Mann–Whitney test (p). The Wilcoxon rank sum test (p) was used to assess the significance of the changes in each of the groups during the study. Differences were considered significant at the level of $p < 0.05$. The presence of a statistical relationship between the parameters was tested using the Spearman's rank correlation coefficient (R).

Ethics

The study was approved by the ethics committee of the Speech Pathology and Neurorehabilitation Center of the Moscow Healthcare Department. Before participating in the study, all patients read the program information sheet and signed an informed consent form.

RESULTS

The average age of the patients in the VR group (20 men and 20 women) was 44.8±15.9 years. The average age of the participants in the control group (10 men and 10 women) was 39.0±14.7 years. Differences in age between patients of the two groups were not statistically significant (p=0.19).

The study cohort consisted of patients with the following diagnoses (according to the International Classification of Diseases, 10th revision): 23 patients (38.3%) with stuttering (F98.5); 16 patients (26.7%) with other mental disorders due to damage to or dysfunction of the brain or due to physical illness (F06.x); 15 patients (25%) with personality and behavioral disorders due to illness, damage to and dysfunction of the brain (F07.x); 3 patients (5%) with sequelae of the COVID-19 coronavirus infection (U07.1) and other viral pneumonia (J12.8); 2 patients (3.3%) with somatoform autonomic dysfunction of respiratory organs (F45.38); and 1 patient (1.7%) with adjustment disorders (F43.2).

Baseline data

At the first examination, patients in both groups demonstrated an average level of state anxiety (Spielberger State Anxiety Inventory), a high and very high level of anxiety on the DASS-21 scale, and average scores on the WAM scale. Patients from the VR group had a higher degree of state anxiety symptoms, manifestations of depression, stress (DASS-21), fatigue (D-FIS), and also characterized their well-being, activity, and mood (WAM scale) lower. However, significant differences were observed only for two parameters of the WAM questionnaire (lower assessments of well-being (WAM-W) and mood (WAM-M) in the VR group) (Table 1).

The average values of physiological parameters at the first measurement in the experimental group were as follows: systolic blood pressure, 124.87±11.62 mmHg; diastolic, 79.37±10.32 mmHg; pulse rate, 70.87±12.34 units.

Changes in scale parameters in the groups during the study (intergroup comparison)

A single VR session led to a significant improvement in the well-being and mood of patients according to the WAM questionnaire, and it also reduced depression, anxiety, and stress according to the DASS-21 scale. After the final session of the VR course and five days after, the patients showed statistically significant positive changes in all studied psychometric parameters (Table 2).

Table 1. Results of the psychometric assessment of patients at the first measurement (baseline), *M±SD*

Scale	Experimental group (VR)	Control group	Significance of differences, *p*
Spielberger State Anxiety Inventory	42.93±11.43	39.45±9.87	0.28
DASS-21	22.05±16.12	16.76±11.91	0.27
D-FIS	12.05±9.31	7.01±4.29	0.22
WAM-W	44.30±14.54	53.7±10.91	0.01*
WAM-A	42.50±11.89	47.9±10.94	0.08
WAM-M	48.28±13.88	56.05±11.07	0.02*

Note: The asterisk (*) marks the statistical significance of differences at $p < 0.05$.

Table 2. Values of the scale parameters at time of visits and significance of changes (*p*) compared with the first measurement in the VR group, *M±SD*

Scale	First measurement (before the first VR session)	After the first VR session	*p*	After a course of five VR sessions	*p*	5 days after completing the VR course	*p*
Spielberger State Anxiety Inventory ↓	42.93±11.43	40.83±9.6	0.94	39.05±9.45	0.006*	38.54±8.99	0.026*
DASS-21 ↓	22.05±16.12	19.46±15.69	0.04*	16.9±11.9	0.01*	14.18±11.72	0.009*
D-FIS ↓	12.05±9.31	10.65±8.62	0.33	8.0±5.27	0.003*	6.94±4.76	0.006*
WAM-W ↑	44.30±14.54	47.51±14.37	0.01*	50.53±11.4	0.007*	51.67±12.52	0.003*
WAM-A ↑	42.50±11.89	44.41±12.87	0.89	47.05±10.1	0.03*	49.67±9.12	0.0008*
WAM-M ↑	48.28±13.88	50.33±13.58	0.04*	53.03±10.05	0.015*	54.09±10.2	0.023*

Note: The asterisk (*) marks the statistical significance of differences at $p < 0.05$; The arrows (↓) show the direction of the positive changes in the parameter.

In the control group, patients did not show significant changes in the studied parameters compared with the baseline assessment, with the exception of the DASS-21 score by the fifth day of the study. The table of average scale parameter values in the comparison group and the significance of the changes at the time of each visit is given in Table S1 in the Supplementary.

The dynamics of the studied parameters in the experimental and control groups during the study is graphically presented in Figures 3–6.

Comparison of the degree of changes in psychometric parameters (intragroup changes)

Changes in the psychometric parameters compared to their baseline (delta) during the study in the experimental and control groups are presented in Table 3.

On the first day, there were no significant differences between the groups in terms of the changes in psychometric parameters; however, by the fifth day, significant differences were visible in the D-FIS score (severity of the fatigue symptom): a more pronounced reduction in the symptom was observed in the group of patients who had undergone a course of relaxing VR sessions (Figure 7).

At the follow-up visit (five days after the completion of a course of five VR sessions), the experimental group showed significantly more pronounced positive changes according to the WAM questionnaire in terms of well-being and activity (Figure 8).

Changes in physical parameters as a result of sessions of virtual reality

One of the objectives of the study was to investigate changes in the physical parameters (blood pressure and pulse rate) as a result of undergoing VR-relaxation. The average values of systolic, diastolic blood pressure and pulse rate before and after undergoing VR sessions are presented in Table 4 (after the first session) and in Table S2 in the Supplementary (after the second and subsequent sessions).

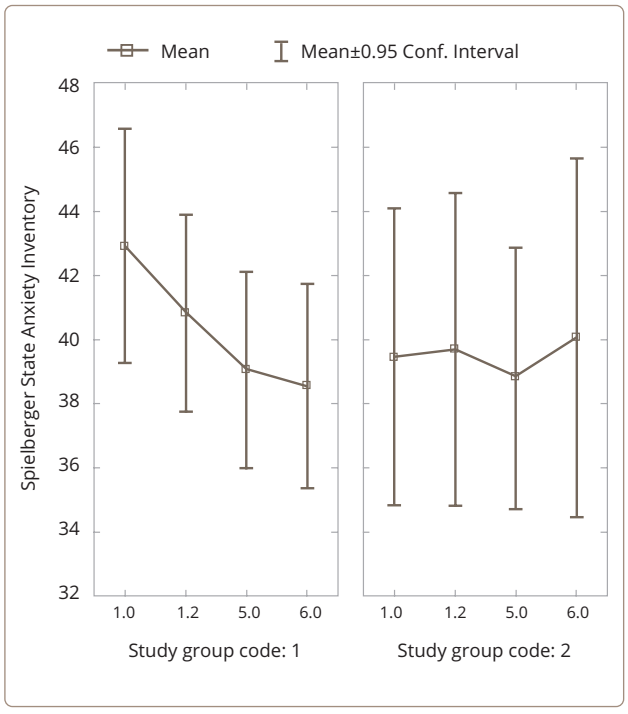

Figure 3. Changes in the Spielberger State Anxiety Inventory parameters in the experimental and control groups during the study.

Note: Designations here and in Figures 4–6: group code in study 1 — experimental group (VR), group code in study 2 — control group; 1.0 — baseline examination, 1.2 — assessment after the first VR session, 5.0 — assessment after a course of five VR sessions, 6.0 — assessment 5 days after the completion of the course of VR sessions in the experimental group and the corresponding points in the control group.

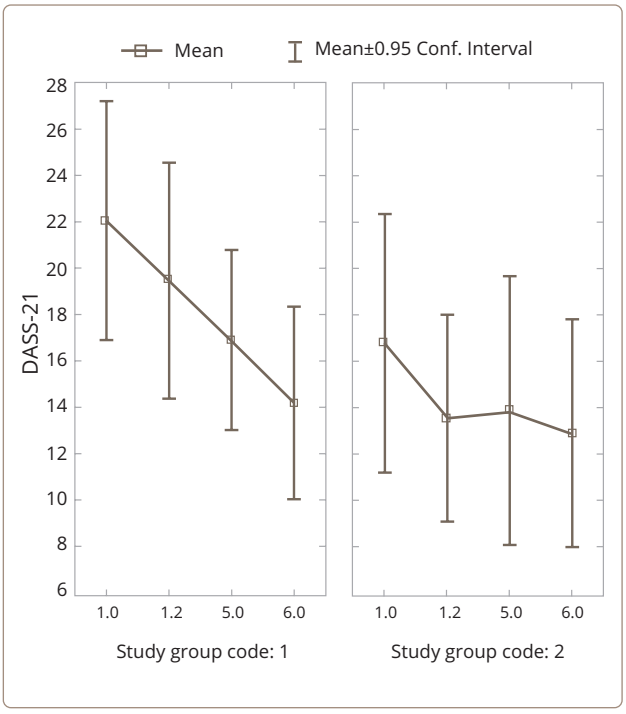

Figure 4. Changes in the DASS-21 parameters in the experimental and control groups during the study.

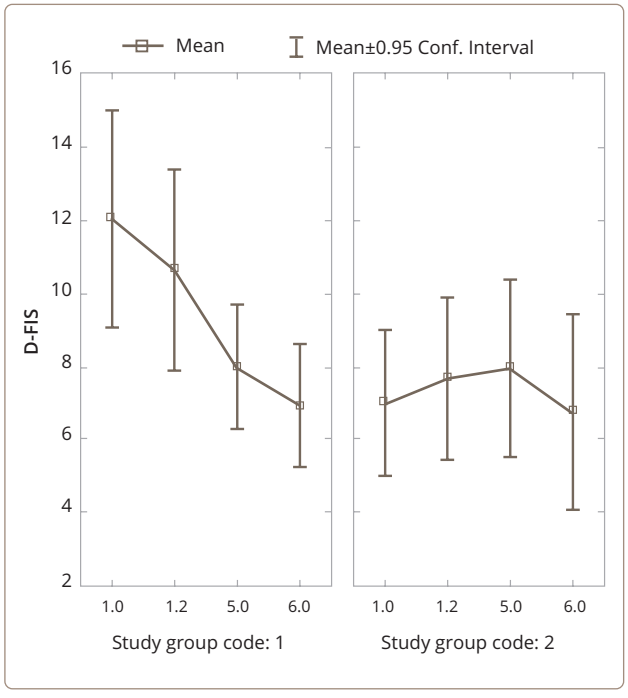

Figure 5. Changes in the D-FIS parameters in the experimental and control groups during the study.

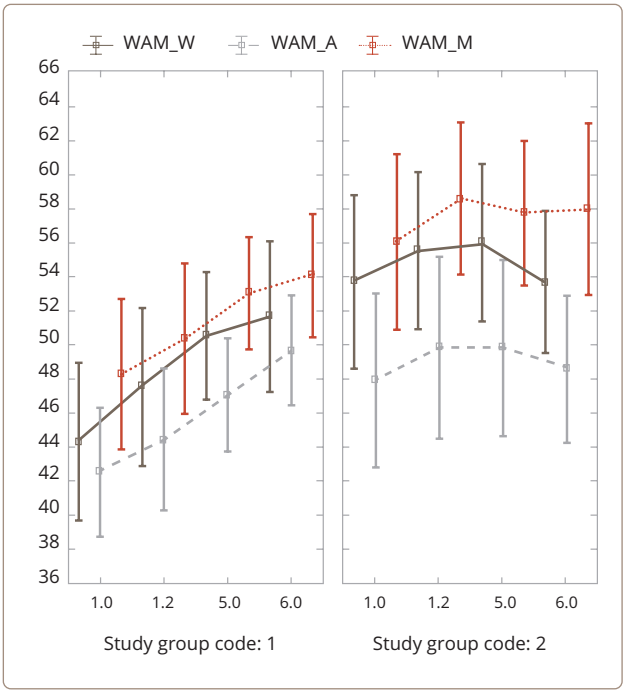

Figure 6. Changes in the WAM parameters in the experimental and control groups during the study.

Table 3. Changes in psychometric parameters and the significance of differences (*p*) between them in the experimental and control groups during the study, *M±SD*

Scale	First day		Fifth day		Long-term	
	VR group	Control group	VR group	Control group	VR group	Control group
Spielberger State Anxiety Inventory	–2.1±7.36	0.1±4.56	–3.82±7.55	–0.65±6.73	–3.67±8.02	–0.38±6.31
	p=0.262		*p*=0.194		*p*=0.14	
DASS–21	–2.0±5.36	–0.06±4.38	–5.03±10.42	–2.84±5.67	–5.58±11.26	–1.56±6.93
	p=0.256		*p*=0.883		*p*=0.466	
D–FIS	–1.4±4.6	1.0±3.78	–3.9±6.89	0.95±3.89	–3.73±6.68	0.006±4.44
	p=0.167		*p*=0.023*		*p*=0.123	
WAM-W	3.26±7.52	0.05±6.37	5.95±13.05	2.3±5.39	6.85±13.89	–1.63±6.21
	p=0.191		*p*=0.173		*p*=0.0034*	
WAM-A	1.92±7.26	–0.11±5.73	4.24±13.06	1.9±7.99	6.67±9.9	–0.69±5.9
	p=0.185		*p*=0.279		*p*=0.014*	
WAM-M	1.59±4.6	0.39±4.09	4.71±11.04	1.7±8.44	4.88±11.28	0.5±6.06
	p=0.389		*p*=0.19		*p*=0.207	

Note: The asterisk (*) marks the statistical significance of differences at $p < 0.05$.

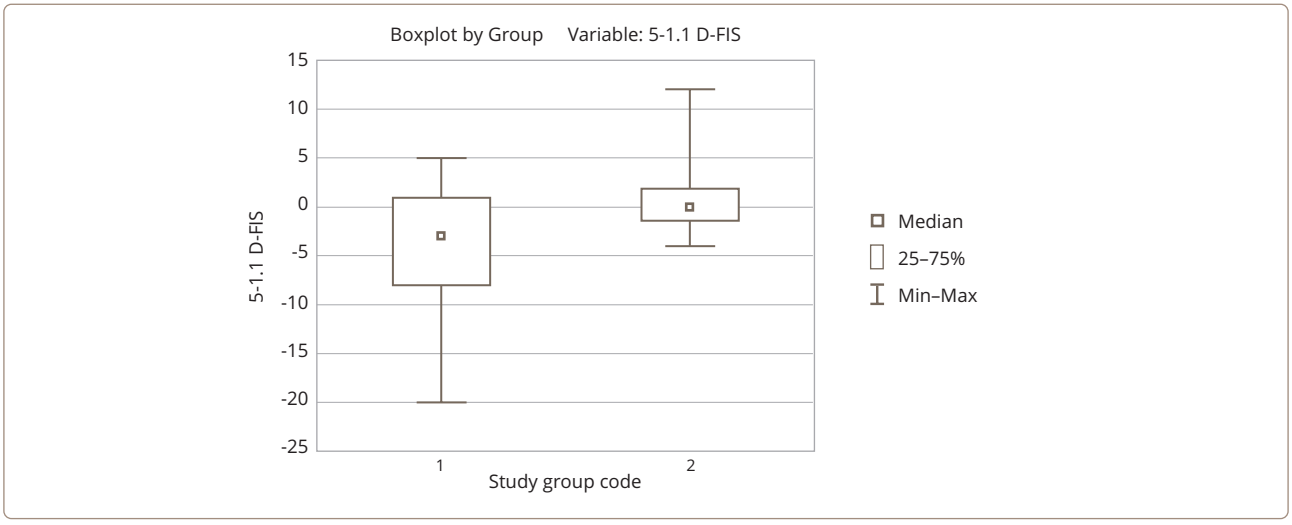

Figure 7. Changes in the D-FIS score between the first measurement and on the fifth day in the experimental (1) and control (2) groups.
Note: The D-FIS score is an inverse scale: higher values mean greater symptom severity, so the lower the delta (visit 5 minus visit 1.1) the better.

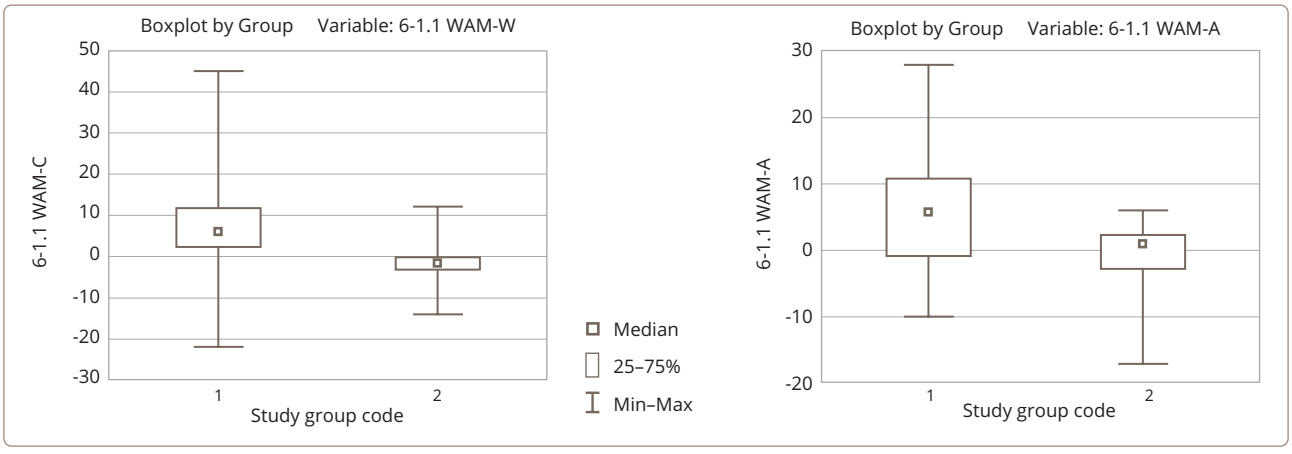

Figure 8. Changes in the WAM scale parameters between the first measurement and the final measurement in the experimental (1) and control (2) groups.

Table 4. Blood pressure and pulse rate before and after the first VR session (*n*=40) and the significance of changes (*p*), *M*±*SD*

Stage	Blood pressure, mm Hg		Pulse rate, units
	systolic	diastolic	
Before the session	124.87±11.62	79.37±10.32	70.87±12.34
After the session	120.03±13.05	76.68±9.23	68.21±9.66
p	0.0008*	0.016*	0.0002*

Note: The asterisk (*) marks the statistical significance of differences at $p < 0.05$.

There is a significant decrease in all parameters in most cases as a result of undergoing the VR program. The decrease in blood pressure was more pronounced in individuals with initially higher blood pressure. In a subgroup of 11 such patients at the final VR session (5 patients with high-normal blood pressure according to the World Health Organization classification of hypertension, 4 patients with grade I hypertension, 2 patients with grade II hypertension), the decrease in blood pressure was even more pronounced (Table 5).

It was also found that for patients with a systolic pressure of 130 or higher before the first VR session, a more pronounced blood pressure decrease after the VR session (at the first visit) meant more pronounced changes on the Spielberger State Anxiety Inventory; i. e., patients with high blood pressure simultaneously showed a reduction in both BP and anxiety (R=0.52).

DISCUSSION

Main findings

The conducted study provides empirical confirmation of the efficacy of the VR relaxation scenario for patients with anxiety and bad mood in a hospital setting. Comparison of the psychometric parameters of patients who underwent a course of VR sessions with patients from the control group shows a clear advantage in terms of positive changes in the first group. There is a significant benefit that accumulates and remains after the completion of the course in terms of improvement regarding anxiety, fatigue, bad mood, various aspects of well-being in the VR group, while patients in the control group showed no significant changes in these parameters throughout the entire study period. The psychological benefit of VR sessions was also reflected in the physiological parameters: blood pressure and pulse rate. Interestingly, the more pronounced the disorders at the beginning of the study were, the more significant the improvement in the patients' condition in terms of both their mental status and autonomic disorders proved.

Table 5. Blood pressure before and after the fifth VR session and the significance of the changes (*p*) in the subgroup of patients with elevated and high blood pressure (*n*=11)

Stage	Blood pressure, mm Hg	
	systolic	diastolic
Before the session	140.55±9.35	86.64±6.47
After the session	124.63±11.96	80.27±12.23
p	0.003*	0.02*

Note: The asterisk (*) marks the statistical significance of differences at $p < 0.05$.

Strengths and limitations of the study

This study was the first study of the efficacy of the VR relaxation scenario Flow in a clinical sample. The positive aspects of the study also include the significant number of participants in the program, sufficient psychometric tools for pilot testing of the hypothesis put forward, and the presence of a comparison group. The study design allowed us to investigate the effects of not only a single VR session, but also the whole course, as well as the stability of the achieved improvement in patients. The limitations of the study are the clinical heterogeneity of the studied cohort of patients, the lack of consideration of the diagnosis impact and the contribution of the pharmacotherapy received by the participants to the observed changes.

Comparison with the existing literature

A wide review of VR studies [32] published between 2000 and 2020 and indexed in major electronic databases (a total of 28 studies analyzed) confirms the effectiveness of using various programs based on VR technology for the treatment of many negative mental conditions, including post-traumatic stress disorder, specific phobias, and social anxiety.

A number of systematic reviews highlight the application of VR methods in a hospital setting. VR instruments have been shown to be effective in relieving pain and reducing

preoperative anxiety in adult patients [33], as well as in a group of adolescent patients [34].

It should be noted that a significant portion of meta-analytical studies using VR technologies do not distinguish between the content of the software, taking into account both virtual games and 3D trips and programs developed specifically for certain therapeutic tasks, although it would seem reasonable to expect the effectiveness of the latter to be higher. In this sense, a direct correlation of the results of various studies may be, to some extent, incorrect from a methodological point of view.

The positive aspects of VR technology also usually include its good tolerance by patients, a high level of involvement of participants, and the possibility of reducing the drug load [35, 36]. Wide introduction of the technology at this stage is limited by the rather high cost of equipment and, to a greater extent, the lack of proven tools for solving specific therapeutic problems and the high costs of their development.

In general, the results of this study are consistent with those of other studies, which also show that the use of tools based on VR technology is effective in addressing various manifestations of anxiety and psychological distress.

The positive results obtained from the Flow pilot study allow us to be optimistic about the prospects of the VR platform in both clinical and outpatient practice. There could be future studies on other samples (including clinical ones) or new scenarios developed within the platform.

CONCLUSION

The results of this study show that the use of the VR relaxation scenario Flow is an effective and promising tool for reducing anxiety and affective symptoms in non-psychiatric inpatients and can be recommended for inclusion in a care program in medical institutions.

Article history:
Submitted: 28.10.2022
Accepted: 14.02.2023
Published Online: 16.03.2023

Acknowledgments: The authors express their gratitude to the employees of Viartech Development LLC: Flow project manager A.I. Konovalov for coordinating the study process; P.A. Dorofeev, A.V. Melnik, V.O. Konyakhin for administration of the process of using the VR-capsule during the study; T.V. Kochneva, laboratory research assistant of the laboratory of psychopharmacology at the Mental Health Research Center, for participation in creating the electronic database; to the doctors and staff of the Speech Pathology and Neurorehabilitation Center of the Moscow Healthcare Department for help and feedback on the use of the VR-capsule in the treatment process.

Authors' contribution: T.A. Lepilkina: development of the study design and protocol, creation and statistical analysis of the database, writing the text of the manuscript; A.G. Beniashvili, R.A. Cheremin: setting objectives and development of the study design, discussing the results and drawing conclusions, editing the text of the manuscript; N.G. Malyukova: selection and inclusion of patients in the study, creation of the study groups, psychometric examination of patients, coordination of the study process; M.A. Morozova: development of the study design, analysis of the data obtained and editing of the text of the manuscript; M.A. Bogdanov, S.V. Rodkina, M.N. Eip: selection, inclusion and psychometric examination of patients; D.S. Burminsky, S.S. Potanin, G.E. Rupchev: analysis of the obtained data and editing of the text of the manuscript. All authors have made a significant contribution to the study and preparation of the article and have read and approved the final version before publication.

Funding: The research was carried out without additional funding.

Conflict of interest: The authors declare no conflicts of interest.

Supplementary data
Supplementary material related to this article can be found in the online version at doi: 10.17816/CP221

For citation:
Lepilkina TA, Beniashvili AG, Cheremin RA, Malyukova NG, Morozova MA, Bogdanov MA, Burminskiy DS, Potanin SS, Rodkina SV, Rupchev GE, Eip MN. Efficacy of a relaxation scenario in virtual reality for comorbid symptoms of anxiety and asthenia in a general hospital setting: a pilot comparative randomized open-label study. Consortium Psychiatricum. 2023; 4(1):CP221. doi: 10.17816/CP221

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Modern Approaches to the Diagnosis of Cognitive Impairment and Alzheimer's Disease: A Narrative Literature Review

Современные подходы к диагностике когнитивного снижения и болезни Альцгеймера: нарративный обзор литературы

doi: 10.17816/CP716

Review

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ABSTRACT

BACKGROUND: The aging of the world's population leads to an increase in the prevalence of age-related diseases, including cognitive impairment. At the stage of dementia, therapeutic interventions become usually ineffective. Therefore, researchers and clinical practitioners today are looking for methods that allow for early diagnosis of cognitive impairment, including techniques that are based on the use of biological markers.

AIM: The aim of this literature review is to delve into scientific papers that are centered on modern laboratory tests for Alzheimer's disease, including tests for biological markers at the early stages of cognitive impairment.

METHODS: The authors have carried out a descriptive review of scientific papers published from 2015 to 2023. Studies that are included in the PubMed and Web of Science electronic databases were analyzed. A descriptive analysis was used to summarized the gleaned information.

RESULTS: Blood and cerebrospinal fluid (CSF) biomarkers, as well as the advantages and disadvantages of their use, are reviewed. The most promising neurotrophic, neuroinflammatory, and genetic markers, including polygenic risk models, are also discussed.

CONCLUSION: The use of biomarkers in clinical practice will contribute to the early diagnosis of cognitive impairment associated with Alzheimer's disease. Genetic screening tests can improve the detection threshold of preclinical abnormalities in the absence of obvious symptoms of cognitive decline. The active use of biomarkers in clinical practice, in combination with genetic screening for the early diagnosis of cognitive impairment in Alzheimer's disease, can improve the timeliness and effectiveness of medical interventions.

АННОТАЦИЯ

ВВЕДЕНИЕ: Старение населения по всему миру ведет к увеличению распространённости ассоциированных с возрастом заболеваний, в том числе и когнитивных расстройств. На стадии деменции терапевтические вмешательства, как правило, малоэффективны. Поэтому в фокусе внимания современных исследователей и клиницистов — поиск способов ранней диагностики когнитивных расстройств, в том числе, с использованием биологических маркеров.

ЦЕЛЬ: Целью данного обзора литературы является анализ научных исследований, посвященных современному состоянию лабораторной диагностики болезни Альцгеймера, в том числе на ранних этапах развития когнитивных расстройств, с использованием биологических маркеров.

МЕТОДЫ: Авторы провели описательный обзор научных исследований, опубликованных в период с 2015 по 2023 год. Были проанализированы работы, представленные в электронных базах данных PubMed и Web of Science. Для обобщения полученной информации был использован описательный анализ.

РЕЗУЛЬТАТЫ: Рассмотрены биологические маркеры крови и ликвора, преимущества и недостатки их применения. Также описаны наиболее перспективные нейротрофические, нейровоспалительные и генетические маркеры, в том числе модели полигенного риска.

ЗАКЛЮЧЕНИЕ: Использование биомаркеров в клинической практике будет способствовать ранней диагностике когнитивных расстройств при болезни Альцгеймера. Генетический скрининг способен повысить выявляемость патологических изменений на доклиническом этапе, когда явные симптомы когнитивных нарушений еще не проявились. В совокупности активное использование биомаркеров в клинической практике в комбинации с генетическим скринингом для ранней диагностики когнитивных расстройств при болезни Альцгеймера способно повысить своевременность и эффективность медицинского вмешательства.

Keywords: *biomarkers; Alzheimer's disease; dementia; diagnosis; cognitive impairment; polygenic risk*
Ключевые слова: *биомаркеры; болезнь Альцгеймера; деменция; диагностика; когнитивные расстройства; полигенный риск*

INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia associated with progressive cognitive decline. The pathogenesis of the disease is related to molecular disruptions resulting in neuronal dysfunction and death, synaptic loss, gliosis, and neuroinflammation. AD-associated abnormalities progress quite rapidly and cause gradual maladaptation of the patient, which imposes a burden not only on the patient's immediate family, but also on the healthcare system in general. According to the World Alzheimer's Report 2015, 46.8 million people suffer from dementia worldwide. This number is expected to reach 131.5 million people by 2050 [1].

Early stages of AD may come with no obvious clinical manifestations, which makes it difficult to diagnose and undertake timely medical intervention, which is most effective at the pre-dementia stages. When making a diagnosis, a clinical practitioner evaluates the patient's history data, takes into account the family history of dementia in first-degree relatives, the physical examination and neurological examination findings, as well as the results of laboratory and imaging tests [2]. It is important to rule out endocrine and metabolic disorders, vitamin deficiencies, possible consequences of infectious diseases and cases of alcohol abuse, including psychoactive substance and drug abuse. In some cases, neuroimaging can reveal morphological changes in the central nervous system (CNS) that are not detected during clinical examination [2]; however, in the case of AD, its use is also not always informative enough due to the non-specificity of the observed structural disorders. A neuropsychological evaluation using the Mini-mental State Examination (MMSE), Montreal

Cognitive Assessment (MoCA), and space-Cog test supplements the results of the patient assessment [3].

At early stages of AD, when the clinical manifestations of the disease may not be sufficiently visible to reach a correct diagnosis, it is advisable to rely on the results of laboratory tests and genetic screening tests, in addition to clinical evaluation findings. The introduction of specific biochemical markers (biomarkers/markers) into routine clinical practice should help detect the onset of AD and trigger the required medical interventions in a timely manner. Our existing biomarker panel is very limited. In most cases, laboratory tests are limited to ruling out somatic and infectious causes of cognitive decline; in rare cases, blood or CSF tests for the β-amyloid level are performed. Therefore, the search for, study, and validation of AD biomarkers, as well as their active implementation in routine clinical practice, is a relevant issue faced not only by scientists, but also by clinical practitioners all over the world.

The aim of this literature review was to analyze scientific papers related to modern laboratory tests for AD, including tests for biomarkers at the early stages of cognitive impairment.

METHODS

The authors have carried out a descriptive review of literature published over the period from 2015 to 2023. This time period was chosen for analysis due to the growing body of research into the early diagnosis of dementia and the discovery of new promising biomarkers. Studies included in the PubMed and Web of Science electronic databases were analyzed. The search queries included the keywords “cognitive impairment”, “dementia”, “Alzheimer’s disease”, “neuroinflammation”, “biomarkers”, “neurotrophic factors”, “genetic markers”, and “polygenic risk”.

The studies were considered eligible if they included an evaluation of the use of biomarkers for the diagnosis of cognitive impairment. The review included studies related to the topic, regardless of their designs. A descriptive analysis was used to summarize the obtained information.

RESULTS

This review included the results of 60 studies related to the topic. Table S1 in the Supplementary provides the characteristics of the included scientific papers; namely, the title, authors, year, country, type of study, methods, and results.

Both blood and CSF biomarkers are used for the diagnosis of AD. The use of blood biomarkers is the most accessible and the least invasive diagnostic method. CSF markers are likely to be more specific; however, a CSF collection procedure is more invasive and not always feasible in primary care clinics. Our review discusses both well-studied biomarkers and markers the diagnostic value of which is yet to be proven. In addition to blood and CSF biomarkers, we have reviewed the use of neuroinflammatory, neurotrophic, and genetic markers of AD.

CSF biomarkers

The diagnostic criteria for AD include the assessment of three classical CSF biomarkers: total tau-protein (T-tau), phosphorylated tau-protein (P-tau), and a 42-amino acid peptide (Aβ42) that reflect the processes of neurodegeneration and the formation of neurofibrillary tangles and amyloid/senile plaques [4]. There is also a number of CSF biomarkers that seem to be promising but require further research. CSF neurogranin has been proposed as a potential neurodegeneration marker associated with AD-associated synaptic dysfunction [5] and having a prognostic value at early stages of the disease [6]. The membrane protein SNAP-25 level in CSF and the SNAP-25/Aβ42 ratio have been proposed as predictors of AD-associated cognitive decline [7]. Apolipoprotein B (apoB) can be a marker of early cognitive impairment associated with AD, particularly, the predisposition to visuospatial disorientation [8]. A recent study conducted in Canada showed that the GAP43 protein, neurogranin, SNAP25 membrane protein, and synaptotagmin 1 are potentially effective biomarkers for predicting AD development 5–7 years before the development of cognitive impairment [9]. As was demonstrated in a meta-analysis by Mavroudis et al., the level of the visinin-like protein 1 (VILIP-1) was significantly higher in AD patients compared to the control group. Compared to patients with mild cognitive impairment (MCI), the level of VILIP-1 was higher in patients with MCI progressing to AD [10].

Blood biomarkers

Blood biomarkers used for the diagnosis of AD include beta-amyloids (Aβ) and their oligomers, the tau protein, neurofibrillary tangles (NFTs), apolipoprotein E (APOE),

microRNAs, exosomes, and gut microbiota markers [11]. The following markers may be used to assess neurodegeneration: a marker for axonal damage — plasma neurofilament (NfL); a marker for glial activation — glial fibrillary acidic protein (GFAP) [12, 13]; β-synuclein [14, 15]; visinin-like protein 1 (VILIP-1) [16, 17]; and the membrane protein SNAP25 [18].

Some authors suggest assessing the levels of iron, ferritin, and cholesterol in the blood as potential markers of cognitive impairment [19]. Other researchers report the potential value of neurogranin as a marker of synaptic dysfunction, the epidermal growth factor (EGF) involved in neurogenesis in adults, as well as pancreatic polypeptide, an increased level of which may be associated with neuronal death [5].

A recent study conducted by Chinese scientists in Hong Kong resulted in the development of a diagnostic panel including 19 plasma proteins, which made it possible to separate patients with AD from the control group with an accuracy of up to 97% [20]. A team of European researchers successfully used a combination of biomarkers (Aß42/Aß40, p-tau181, ApoE4) in two independent cohorts to identify amyloid-positive patients and predict the development of AD [21]. Brazilian researchers have developed a machine learning-based diagnostic panel that includes 12 plasma proteins (ApoB, calcitonin, C-peptide, C-reactive protein, IGFBP-2, Interleukin-3, Interleukin-8, PARC, transferrin, TCP, TLS 1-309 and TN-C) and allows one to predict the slide from MCI to AD-associated dementia within the subsequent four years [22].

Mass spectrometry of a number of candidate biomarkers in serum demonstrated a statistically significant decrease in the levels of afamin, apolipoprotein E, biotinidase, and paraoxonase/arylesterase 1 in AD patients [23]. The combination of mass spectrometry with machine-learning technologies allows one to evaluate the risk of AD development in the subsequent three years in patients with MCI, using a diagnostic panel based on 31 serum biomarkers with an accuracy of ~80%, sensitivity of 79.4%, and specificity of 83.6% [23].

Neuroinflammatory markers

An increase in the concentration of pro-inflammatory markers can also serve as a prognostic risk factor of the development of dementia in AD patients [24]. However, it should be taken into account that brain inflammation can also be associated with many other disorders, including depression and multiple sclerosis [24].

Neuroinflammation leads to the formation of reactive oxygen species (ROS), chemokines, cytokines, and various secondary messengers [25]. Tissue-resident immune cells, CNS glial cells such as microglia, astrocytes, and endothelial cells are involved in the production of inflammatory mediators. Neuroinflammatory reactions lead to immune, physiological, biochemical, and psychological effects.

During the development of AD, a hyperphosphorylated tau protein forms and the accumulation of neurofibrillary tangles in the central nervous system tissues leads to the release of exosomes, which additionally enhance the expression of chemokines, such as the 3X CXCL3 chemokine ligand, and increase the level of the NLRP3 inflammasomes. Then, the synthesis of interleukin-1ß (IL-1ß) is triggered, leading to a neuroinflammatory cascade [26].

Inflammatory markers associated with neuronal damage include cytokines, the transforming growth factor-beta (TGF-β) and IL-1ß, which cause direct synaptic damage to microglia [27]. As a result, the transmission of the synaptic impulse is disrupted and the communication of the neural network deteriorates, which ultimately leads to synaptic dysfunction and neurodegenerative changes.

Based on the data collected by researcher who studied the consequences of neuroinflammation [28], a direct correlation between neuroinflammatory changes and the onset of neurodegeneration resulting in cognitive decline of varying severity may be assumed. Since mental disorders that include cognitive decline are associated with the immune response (namely, microglial activation and production of pro-inflammatory agents), tests for immunological markers may contribute to the prediction of the development of cognitive impairment [28].

According to I.K. Malashenkova et al., the following correlation between changes in the immune status and the development of cognitive impairment exists [29].

All patients with a significant deterioration of cognitive function and the development of dementia of the Alzheimer's type had systemic inflammation at the beginning of the study, which manifested itself in changes in the respective parameters. Particularly, there was an increase in the levels of the C-reactive protein and pro-inflammatory cytokines, namely IL-1β, interleukin-8 (IL-8), and the tumor necrosis factor alpha (TNFa).

Table 1. Changes in the immune status of patients with cognitive impairment [29]

Parameter Diagnosis		Mild cognitive impairment	AD severity		
			mild	moderate	severe
C-reactive protein concentration		↑	↑	↑	↑
IL-1β and TNFα cytokine concentrations		↑	↑	N	N
Humoral immunity	IgG	N	N	↓ in 50% of patients	↓↓
	IgA	N	N	N	↑
Cell-mediated immunity	NK cell count	N	↑↑	↑↑	↑↑

Note: ↑ — increase, ↓ — decrease, ↑↑ — significant increase, ↓↓ — significant decrease, N — no significant changes.

However, these markers are non-specific and a change in their concentrations may be typical for a number of disorders [29] (Table 1).

Neurotrophic markers

The neurotrophin family consists of the nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), as well as the neurotrophins NT-3, NT-4/5, and NT-6. Brain neutrophin level changes are observed in patients with various disorders, such as mental illnesses (e.g., depression and schizophrenia), parasitic diseases of the central nervous system, as well as neurodegenerative diseases such as AD [30]. In this regard, it is reasonable to assume that changes in the concentration of neurotrophins may have a diagnostic value. Do Carmo et al. investigated the NGF metabolic pathway dysregulation in connection with cholinergic dysfunction in AD patients and came to the conclusion that changes can be detected as early as at the preclinical stages of AD, which makes NGF a potentially valuable prognostic marker [31]. Scientists studying changes in the NGF metabolism in AD patients with the Down syndrome came to similar conclusions. The researchers believe that impaired metabolism of NGF may be detected as early as at the stage of MCI [32].

BDNF is a neurotrophin, and low levels of BDNF in the CNS tissues are commonly associated with neurodegenerative disorders [30]. BDNF is usually associated with neuronal survival, synapse formation, neuroplasticity, and changes in the inhibition and excitation mechanisms. The presence of a neurotoxic stimulus and concomitant neurological disorders causes a decrease in the level of BDNF, which manifests itself in cognitive impairment of varying severity [30].

In a recent study conducted in Italy, serum levels of BDNF in patients with MCI and AD were evaluated in association with BDNF gene polymorphisms (Val66Met, rs6265; C270T, rs56164415). Serum BDNF levels were significantly lower in AD patients (p=0.029), especially females (p=0.005). Serum BDNF levels were also shown to be related to the IL-1α and BDNF gene polymorphisms [33]. The researchers showed that high levels of BDNF were associated with a lower risk of neurodegenerative disorders [34]. However, the researchers evaluated the diagnostic value of BDNF differently. In a study by Qian et al., plasma levels of BDNF were decreased at the stage of MCI and increased at the stage of dementia and were dependent on a number of factors such as age, education, and occupation. Therefore, the investigators concluded that plasma levels of BDNF cannot be a reliable marker for early screening and diagnosis of AD [35].

Other neurotrophins also may have a predictive value for the diagnosis of AD. In an animal model of AD, Chinese researchers showed that the NT-3 neurotrophin improved cognitive functions by increasing neuronal differentiation [36]. The value of NT-4/5 in the early diagnosis of AD has not been sufficiently studied and requires further research. A study conducted by Mexican researchers demonstrated an inhibitory impact of NT-4/5 on the effects of BDNF [37].

Genetic markers

The existence of familial Alzheimer's disease (AD) indicates that genetic factors play an important role in the pathogenesis of this disease. The most aggressive type of AD (early-onset AD) is highly likely to be inheritable [38].

The most studied, but not the only one, genetic risk factor of AD is the presence of an ε4 allele of apolipoprotein E (APOE). The incidence of this allele among patients with AD amounts to 20–25% and is known to result in a 3-fold and a 15-fold increase in the risk of developing the disease in heterozygous and homozygous carriers,

respectively [39]. The ε2 allele of the APOE gene is associated with a low risk of AD; ε3 carriers are also significantly less likely to develop dementia compared to ε4 carriers [40]. Isoform-specific effects of apolipoprotein E in the brain affect changes in Aß, the tau protein and other neuroinflammatory, and metabolic markers. However, the exact molecular mechanisms of Aβ regulation evaluated in animal models have not been established so far. It still remains unclear whether the ε4 allele affects the AD pathogenesis by increasing the toxicity or weakening protective functions (or a combination of both). To date, no medicines to treat/prevent the progression of AD affecting the pathways of the APOE4 isoform formation have been developed. The combined therapy of increased lipidation with simultaneously decreasing lipid-free apoE4 would be an appealing approach to prevent the progression of AD. However, it is currently obvious that AD is a multifactorial disorder that is due to the changes in the expression of many various loci [40].

Genome-wide association studies (GWAS) conducted using samples from tens of thousands of AD patients and healthy donors have generated a large amount of AD-related genetic data [41, 42] and identified more than 40 loci associated with the disease [43]. Nevertheless, single nucleotide polymorphisms (SNPs) in the identified loci are likely to have little effect on the risk of developing the disease and cannot be used as independent prognostic markers [43]. This issue is typical for many multifactorial disorders. To assess the influence of genetic factors on disease development and the formation of a certain trait, a polygenic risk score (PRS) was proposed. PRS models assess the cumulative (multiplicative) influence of several SNPs, which are usually selected based on GWAS using special algorithms [44]. Each SNP is assigned an individual coefficient (which is generally a weighted odds ratio), and the PRS is calculated as a sum of the numbers of risk alleles multiplied by the respective coefficients [44].

The first PRS model for AD risk assessment was published in 2005, even before large-scale GWAS. This model includes nine SNPs, including the ε4 allele of APOE [45]. Based on the GWAS data, the PRS models were proposed and 19 to 31 SNPs were included in the most elaborated ones [46–49]. Additional factors may include APOE gene alleles, gender, age, as well as other social and physiological characteristics.

Studies of PRS models have established an association of the values of this parameter with the risk and age of AD and dementia development [48–50], as well as the rate of MCI progression and the risk of it spilling into AD [51–53]. It should be noted that cognitive functions in healthy subjects at different ages have also been shown to be associated with PRS [53–56]. Moreover, PRS has been shown to be associated with structural and functional brain abnormalities, as well as some biochemical parameters typical o neurodegeneration [48, 57, 58], including deposits of amyloid and the tau protein [59–62].

Thus, polygenic models represent a promising tool for identifying people at high risk of developing AD. From the practical viewpoint, these tests are useful in the selection of individual preventive measures and the development of screening strategies. Furthermore, PRS can be effectively deployed when designing clinical studies of AD therapy methods that may prevent progression of the disease; it is assumed that the inclusion of people with high PRS values and, accordingly, a higher risk of AD development into the evaluated cohorts may increase the chances of identifying effective prophylactic strategies [44, 62].

It should be noted that most of the studies of PRS in patients with AD were conducted on Caucasians, and that additional studies will be required to extend the obtained results to other populations [44]. This should be taken into account when using this approach for the multinational Russian population.

DISCUSSION

Diagnostic criteria for AD currently include the assessment of three classical biomarkers (T-tau, P-tau, Aβ42) in the cerebrospinal fluid. They have been the most thoroughly studied and elaborated. There is a number of promising CSF biomarkers (neurogranin, membrane protein SNAP-25, GAP43 protein etc.) which are being actively studied and have potential prognostic value. Blood biomarkers include beta-amyloids (Aβ), the tau protein, neurofibrillary tangles (NFTs), apolipoprotein E (ApoE), etc. They do not provide reliable diagnostic information when assessed separately; however, the assessment of a multiple blood biomarkers panel using mass spectrometry and machine-learning technologies appears promising. The generation of fundamental knowledge that is not oriented toward one biomarker, e.g. Aβ, allows one to use the integrative systematic approach to differentiate between normality and abnormality based on the patient's biomarker profile [63].

Researchers have demonstrated the importance of resorting to biochemical and genetic markers in laboratory diagnostics [2, 27]. Neuroinflammatory biomarkers (interleukins, TNFα, TGF-β etc.) are the most commonly detected in patients with neurodegenerative disorders; however, they suffer from low specificity. The search for specific neuroinflammatory markers and their use in patients with MCI or dementia may be crucial for understanding early stages of neurodegenerative disorders. We believe that the neuroinflammatory markers that have been evaluated to date are of significant prognostic potential and can already be used for diagnosis.

Neurodegenerative disorders are commonly associated with changes in the concentrations of neurotrophins (BDNF, NGF, etc.) and neuroinflammatory markers; however, these changes are not specific enough to enable confident diagnostic decisions. Further research is needed to identify AD-specific neurotrophic biomarkers.

Today, a number of genetic markers are used for genetic screening, primarily, APOE gene polymorphisms, the detection of which predicts the development of Alzheimer's disease with a high probability and can be used in the future for the prescription of targeted therapy. Therapeutic approaches targeting the APOE, including: 1) their effects on the structural properties of apolipoprotein E and interaction with Aß, 2) modulation of APOE levels, and prenylation, 3) the effects on APOE receptors, and 4) APOE gene therapy, are currently being developed using animal models. Moreover, some researchers believe that genetic biomarkers will contribute to a better understanding of the disease pathogenesis [53, 55]. PRS models appear promising for diagnosis and preventive medicine. From the practical viewpoint, these models should be useful in the selection of individual preventive measures and the development of screening strategies. Furthermore, PRS can be effectively used when designing clinical studies of AD therapies that may prevent progression of the disease; it is assumed that the inclusion of people with high PRS values and, accordingly, a higher risk of AD development into the evaluated cohorts may increase the chances of identifying effective prophylactic methods [44, 62]. It should be noted that most of the studies of PRS in patients with AD were conducted on Caucasians, and that additional studies will be required to extrapolate the obtained results to other populations [44]. This should be taken into account when using this approach for the multiethnic Russian population.

Strengths and limitations of the study

Our study covers different types of biomarkers, presents a brief description of their characteristics and potential uses, and includes an overview of the main research areas. The limitation of this study is that a number of suitable studies on the topic could have been missed, since no systematic search strategy was used for the purposes of this review. Therefore, the conclusions drawn in the article may be considered preliminary.

Application of the results

The improvement of diagnostic accuracy using multiple biomarkers determined using various omics technologies is one of our most immediate challenges, the solution of which will facilitate the diagnosis of cognitive impairment, increase the efficacy of therapeutic and rehabilitation measures, and improve prognosis and patients' quality of life. Another relevant issue is the development of modern diagnostic approaches based on the evaluation of a panel of neuroinflammatory and neurotrophic markers. The specific feature of these markers is potential prognostic value at the preclinical stage of cognitive impairment, when timely medical interventions can still prevent or significantly slow down the progression of cognitive decline.

CONCLUSION

The active use of biomarkers in clinical practice, in combination with genetic screening, for early diagnosis of cognitive impairment in Alzheimer's disease can increase the timeliness and effectiveness of medical intervention. However, the development of a comprehensive and effective strategy for the management of AD-associated cognitive impairment requires further research aimed at improving diagnostic accuracy using biological markers, such as neuroinflammatory markers. An important issue that needs to be addressed in the future is not only the search for new biological markers, but also their active introduction into clinical practice.

Article history:
Submitted: 03.02.2023
Accepted: 13.03.2023
Published Online: 27.03.2023

Authors' contribution: All the authors made a significant contribution to the article, checked and approved its final version prior to publication.

Funding: This research was funded by the Moscow Centre for Innovative Technologies in Healthcare, Grant No. 2708-1/22.

Conflict of interest: The authors declare no conflicts of interest.

Supplementary data

Supplementary material related to this article can be found in the online version at doi: 10.17816/CP716

For citation: Ochneva AG, Soloveva KP, Savenkova VI, Ikonnikova AYu, Gryadunov DA, Andryuschenko AV. Modern approaches to the diagnosis of cognitive impairment and Alzheimer's disease: a narrative literature review. Consortium Psychiatricum. 2023;4(1):CP716. doi: 10.17816/CP716

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Celebrating a Storied History: Moscow Preobrazhenskaya Mental Hospital Marks its 245th Anniversary

История одного юбилея: к 245-летию Московской Преображенской больницы для душевнобольных

doi: 10.17816/CP3704

Information

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Mental-health Clinic No. 4 named after P. B. Gannushkin, Moscow, Russia

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ABSTRACT

In 2022, Mental-health Clinic No. 4 named after P. B. Gannushkin, one of the oldest mental health institutions in Russia known as Preobrazhenskaya Hospital before the October Revolution of 1917, celebrated its 245th anniversary. The history of the hospital reflects all stages of the evolution of the basic principles and aspects of mental health care in Russia. On many occasions, the institution served as a platform for eminent researchers and clinicians to achieve scientific breakthroughs and their application in practice. This article is a review of the major milestones in the history of the hospital. It highlights the great achievements of its psychiatrists and presents some previously unpublished archival documents that offer a new perspective on the history of Preobrazhenskaya Hospital.

АННОТАЦИЯ

Одна из старейших психиатрических больниц России — московская Психиатрическая клиническая больница имени П. Б. Ганнушкина (ГБУЗ «ПКБ № 4 ДЗМ»), до революции 1917 года именовавшаяся Преображенской, — в 2022 году отметила свое 245-летие. В истории учреждения отразились все этапы развития основных принципов и форм лечения людей с психическими расстройствами. Больница не раз становилась местом научных открытий и их практической апробации для известных ученых и клиницистов. В статье рассматриваются наиболее значимые для истории становления больницы даты, освещаются важнейшие достижения врачей-психиатров, работавших здесь, а также приводятся данные из архивных документов, не публиковавшихся ранее, что позволяет представить новый взгляд на историю юбилеев Преображенской больницы.

Keywords: *Preobrazhenskaya Hospital; P. B. Gannushkin Hospital; Sabler; Korsakov; Bazhenov*

Ключевые слова: *Преображенская больница; Больница имени П. Б. Ганнушкина; Саблер; Корсаков; Баженов*

INTRODUCTION

In 2022, Mental-health Clinic No. 4 named after P. B. Gannushkin, one of the oldest mental health institutions in Russia known as Preobrazhenskaya Hospital before the October Revolution, celebrated its 245th anniversary. This represents the number of years since Catherine the Great signed a decree establishing the Moscow House of Invalids, where several dozen beds

were set aside for the mentally ill. The document, issued in 1777 [1], laid the foundation not only for Moscow's first specialized institution that could accommodate patients with mental disorders, but also, without exaggeration, for the entire field of Russian psychiatry.

The implementation of the Pinel reform in Russia, the introduction of the concept of "moral treatment", the first scientific conferences and open clinical discussions, all these stages in the evolution of the basic principles and aspects of mental health care have found their reflection in the history of Preobrazhenskaya Hospital over the past 245 years. This is why Vasily Gilyarovsky poetically referred to the Hospital as "the cradle of Russian psychiatry" [2].

Each page in the history of Preobrazhenskaya Hospital is not only an impressive list of achievements and innovations, but also a unique gallery of distinguished names [3–7]. It served as a basis for the greatest medical luminaries of the time, such as V. F. Sabler, V. R. Butzke, V. A. Gilyarovsky, N. N. Bazhenov, A. V. Snezhnevsky, D. E. Melekhov, T. I. Yudin, S. G. Zhislin, and G. Y. Avrutsky, from which to make their scientific discoveries and validate them in practice; this was also the place where such luminaries of Russian psychiatry as S. S. Korsakov, A. U. Frese, E. K. Krasnushkin, P. E. Snesarev, A. S. Tiganov, and I. Y. Gurovich, and many others, began their medical careers.

It is a well-known and undisputed fact that Preobrazhenskaya Hospital was the first (and almost only one until the end of the 19th century) psychiatric hospital to appear in Moscow. But historians and researchers in psychiatry have spent more than 100 years trying to dig up documents that could allow them to determine the exact year of its founding.

Starting in the second half of the 19th century, the question has frustrated many eminent physicians of Preobrazhenskaya Hospital, including S. I. Steinberg [8], I. V. Konstantinovsky [9], N. N. Bazhenov [10], M. A. Dzhagarov [11], and A. B. Alexandrovsky [12]. Their work can now help us to form a fairly comprehensive view of how the State and society gradually, step by step, developed an awareness of what such an independent institution as a psychiatric hospital was all about. They painstakingly assembled scattered documents and facts to finally pinpoint with certainty the day it all began and the events that could be considered key milestones in the hospital's history.

FROM FIRST MENTIONS TO 19th CENTURY REFORM

The first building that hosted Preobrazhenskaya Hospital, originally known as Moscow Dolgauz, opened its doors on June 15, 1808. In the 20th century, it became routine to trace all anniversaries of the institution back to that date. But is that right? Could the mere fact that the hospital acquired its own building be considered the seminal event of the first inpatient psychiatric hospital in Moscow?

On July 13, 1777, Catherine the Great signed a decree mandating the opening of the House of Invalids in Moscow, with one of its "wards" dedicated to the care of the mentally ill. This is the date that, 100 years later, the doctors at Preobrazhenskaya Hospital referred to as the starting point in the history of their institution [8]. One of their main arguments was the fact that, on May 17, 1792, Catherine the Great issued a decree [1] establishing for the first time the position of Special Doctor at the mental health hospital. Hence, this decree confirms that this type of social institution for people with mental disorders already existed in 1792.

According to the decree signed by Catherine the Great, the primary role in the observation of patients was assigned to the warden, who was in charge not only of the guards (retired soldiers), but also of the doctor responsible for the professional supervision of patients. In reality, however, the staff physician had to juggle work at the mental health hospital with his duties in the nursing home, the hospice, and the almshouse. As a result, his attention was limited to those patients who had a chance of recovery [13].

When assessing the efforts of the first doctors at the mental health hospital, such as F. Raschke, then C. Pouliard, A. Blimmer, J. Karas (and all this happened long before the hospital had its own building), N. N. Bazhenov wrote in his book about Preobrazhenskaya Hospital: "It is important to note that even then there was a firm belief that the insane person was a patient, with all that such a conclusion entailed, including examination by a physician, admission to the mental health hospital for treatment (no matter how crude and primitive that treatment might have been), and finally discharge when the physician was satisfied that the goal of admission (a cure) had been achieved" [10].

Other doctors at Preobrazhenskaya Hospital also left their mark in the history of Russian psychiatry of the 19th

century. For example, Zinovy Ivanovich Kibalchich, Chief Doctor of the hospital in 1811–1828, left us a documented description of the prevailing realities in a mental hospital at the beginning of the 19th century. In his 1821 article "Report on the House of the Insane in Moscow and the Methods of Treatment Used There" published in the Journal of the Imperial Philanthropic Society (issue No. 11, 1821), he not only described in detail Moscow Dolgauz and the methods of treatment used there, but he was also one of the first to point out the existence of mental disorders that are now referred to as "borderline conditions" [14].

Vasily Fedorovich Sabler, chief doctor of Preobrazhenskaya Hospital in 1828–1871, was a true "revolutionary" in the early history of psychiatric care in Russia (Figure 1).

A brilliant clinician and talented scientist, V. F. Sabler provided evidence for the nosological independence of progressive paralysis, described its accompanying mental and neurological disorders, and developed humanistic principles of individual approach to patients. He was one of the first to hypothesize that some forms of illness can evolve into others, and that severe somatic illness accompanied by high body temperature (fever) can contribute to the cure of psychosis.

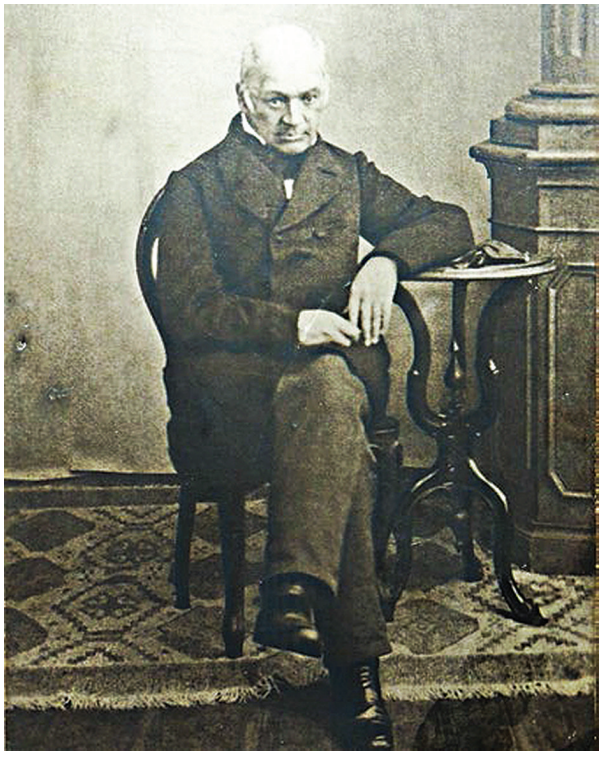

Figure 1. Vasily Fedorovich Sabler (1797–1877) — chief doctor of Preobrazhenskaya Hospital in 1828–1871.

In the history of Preobrazhenskaya Hospital, V. F. Sabler played an equally prominent role as an outstanding manager. With a radical reform of the hospital's management system, he ensured that the Chief Doctor would become the actual head of the institution. He supervised all areas of the hospital's activities and prepared reports on the clinic that were published in the press (including in Europe).

This administrative reform marked a dramatic shift in attitudes toward the mentally ill. V. F. Sabler was greatly influenced by Philippe Pinel's concept, which led him to completely overhaul the patient management system, finally replacing the chains used on violent patients with straitjackets and restraint chairs with straps.

It was the first instance when treatment was given priority over charity. This included the first patient histories (known as "case sheets", see Figure S1 in the Supplementary) and prescription books. Depending on the course of their disease, patients were categorized as acute or chronic and treated using a different therapeutic approaches.

The new emphasis was not only on the medical observation of the patients, but also on their moral challenges and re-education. Patients were no longer seen as "dangerous madmen" but as "unreasonable children" who needed proper care and exercise. That is why occupational therapy was considered so important. According to the instruction "On the Exercises for the Sick People Placed at the Mental Health Hospital" published in 1834, each patient was assigned a strictly individual occupation. It was then that Preobrazhenskaya Hospital established a sewing shop, a tailor's shop, a shoemaker's shop, a dyer's shop, a paint shop, a plasterer's shop, and a vegetable garden. The women could also knit socks and embroider canvas.

V. F. Sabler initiated the effort to draft legislation on the mentally ill, which provided the impetus to address a long overdue problem in the patient examination process. For centuries, medical matters had been handled by officials with no expertise in diagnosing mental illness, and during the reign of Nicholas I, the authorities began committing patients to institutions "pending further orders" rather than "pending recovery", as had always been the case. It was not until February 18, 1835, that a decree was issued establishing a procedure

for forensic psychiatric examination that required convincing evidence of mental illness from credible medical experts.

In 1841, the so-called "special patient examination procedure" was introduced and implemented for the first time at Preobrazhenskaya Hospital. If in St. Petersburg the "lunatics" continued to be transported to the Provincial Board, in Moscow the "subjects" were now sent to Preobrazhenskaya Hospital for "expert examination" and placed in a ward specially purposed for such subjects in a section of St. Catherine's Almshouse. Membership in the Patient Examination Committee was also established at that time and did not change until 1917. It included the hospital doctor, his/her assistant, the provincial marshal of the nobility, the chief of the district police or the head of the city. Patients were discharged only after a new examination, which could take place at the end of a two-year "observation" period, and this period could be shortened only by special decision of the Senate.

The hospital owes both its name, Preobrazhenskaya, and the confirmation of its new official status as a medical institution to V. F. Sabler. It was he who on May 31, 1838, petitioned Emperor Nicholas I to sign a decree renaming the Moscow Dolgauz as the Preobrazhenskaya Mental Hospital.

Assessing the changes that took place in the hospital during the first hundred years of its existence, historians of psychiatry are quite right to note that as early as the middle of the 19th century Preobrazhenskaya Hospital had made the transition from a "charity house" to an in-patient psychiatric institution and had evolved into "the center of not only practical but also scientific psychiatry, which became the tradition of the Moscow psychiatric school, distinguishing it from the St. Petersburg psychiatric school" [7].

These changes, most of which were introduced during V. F. Sabler's leadership, allowed Samuil Ivanovich Shteinberg (the hospital's chief doctor in 1872–1877) to begin work on the institution's first collection of scientific papers in the run-up to the centennial of Preobrazhenskaya Hospital in 1877. The preserved documents ("Preobrazhenskaya Hospital Office File on the Centennial Anniversary…") show that the preparations for this anniversary had begun well in advance. As early as in February 1876, the chief physician, S. I. Shteinberg, wrote a letter to the trustees of Preobrazhenskaya Hospital with a detailed plan of the celebration. A circular letter was sent to the staff instructing S. S. Korsakov, N. I. Derzhavin, and V. R. Butzke to begin preparing articles identifying the major milestones in the history and development of the hospital (Figure S2 in the Supplementary).

In the 1870s and 1880s, the hospital attracted a cadre of brilliant and exceptionally gifted young physicians who introduced the most advanced methods of patient care into existing medical practice. First of all, this applies to Sergey Sergeyevich Korsakov, the founder of the nosological branch of psychiatry, the creator of the Moscow scientific school and the author of a classic course in psychiatry [4, 5]. His name is closely connected with the history of the "therapeutic revolution" at Preobrazhenskaya Hospital. The energy and reputation of S. S. Korsakov helped to complete and irretrievably establish "moral treatment" at the hospital and the "open door" policy (from 1889), followed by out-of-hospital care, which radically changed the entire approach to patients.

20th CENTURY: TRANSFORMATIONS AND ACHIEVEMENTS

Looking back, it is impossible to ignore one obvious fact: almost all the chief doctors of Preobrazhenskaya Hospital in the period before the Russian Revolution of 1917 acted as reformers of the entire Russian psychiatric care system. An honorable place in this gallery of illustrious figures is occupied by Nikolai Nikolaevich Bazhenov, chief doctor of the hospital in 1904–1917 (Figure 2).

Preobrazhenskaya Hospital owes its vast expansion and the introduction of the then — revolutionary system of "advanced care" to this fascinating figure of Russian psychiatry, outstanding clinician, ingenious manager, and respected teacher.

In the new "advanced care" system, the uneducated wardens and nannies were replaced by young medical interns and sisters of mercy. The doors to the wards were unlocked, the bars on the windows were replaced with tempered glass, and the straitjackets were displayed as museum pieces [15–17]. To ensure that patients were under continuous and competent supervision, the interns were required to live in the hospital, rotate on round-the-clock duty, welcome new admissions, and complete patient histories and observation diaries. All direct patient care was assigned to mid-level medical

staff. Thirty-two sisters of mercy washed and fed the patients, gave them baths, accompanied them on walks, etc. Each ward had a head nurse who distributed medications, served lunch and dinner, was in charge of laundry, and performed other household duties. Nannies and servants were assigned only janitorial duties. In the spirit of those times, the hospital widely applied a system of moral influence, a prototype of today's psychosocial therapy that included respectful treatment and support of patients, their socialization, and involvement in various activities.

At the beginning of the 20th century, with N. N. Bazhenov's contribution, the hospital was transformed into a research and treatment institution, which became a center of advanced psychiatric knowledge. The scope of N. N. Bazhenov's innovations is quite impressive: in just a few years the clinic, where at the turn of the century treatment of patients resembled more that in a prison than in a medical institution, was transformed into a modern hospital, on par with the best that Europe could offer [15–17].

Preobrazhenskaya Hospital was also the place where the Law on the Mentally Ill, a revolutionary act for its time, was proposed 80 years before the adoption of the Russian Federal Law on Psychiatric Care in 1992. The legal principles outlined by N. N. Bazhenov at the first congress of the Russian Union of Neuropathologists and Psychiatrists in 1911 are still relevant today:

"The following issues need to be brought to the forefront of mental health care and legislated:

a) The principle of extending state care to all mentally ill people in the country, and specifying the measures to implement this task and the central and local authorities responsible for these tasks.
b) Conditions for allowing treatment at home in the patient's own family.
c) Sufficient safeguards must be in place to ensure that the principles of inviolability of the person and individual liberty can only be violated when the mental illness of the person in question makes this imperative" [18].

N. N. Bazhenov is also connected with the first commemoration of the foundation of the hospital celebrated in the 20th century. In December 1909 the 100th anniversary of the opening of the first building hosting Preobrazhenskaya Hospital on Matrosskaya Tishina Street was commemorated in gushing but solemn fashion, with the participation of the general public.

By that time the clinic had already received a plot of 11 dessiatins of land with the two and three-story buildings of the former Kotov factory (known as "Kotov's Half") (Figure 3).

The factory buildings were refurbished, and a dormitory for the staff was equipped with ventilation, plumbing, and even central heating, which allowed N. N. Bazhenov to write proudly that "now Preobrazhenskaya Hospital has such premises for the staff that few Russian or even Western European hospital institutions can boast of" [10].

However, the problem of overcrowding could be solved only by the construction of new buildings on Kotov's Half, which required additional funds. So, N. N. Bazhenov decided to organize a gala evening for the city's dignitaries on the former Kotov estate.

The day of the anniversary celebration was packed with events, including a solemn liturgy and breakfast for 300 guests; in the afternoon, there was a large concert by professional musicians from Moscow; a festive tea ceremony for patients, distribution of anniversary souvenirs, such as cups with the hospital insignia;

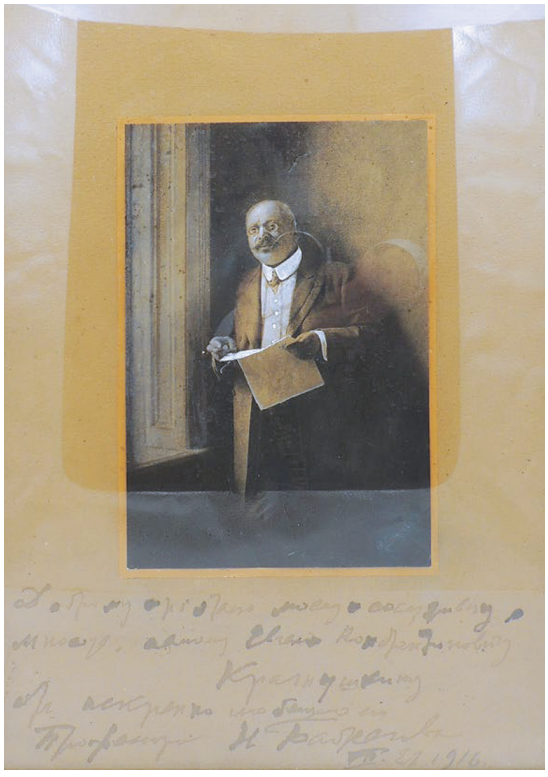

Figure 2. Nikolai Nikolaevich Bazhenov (1857–1923) — chief doctor of the hospital in 1904–1917.

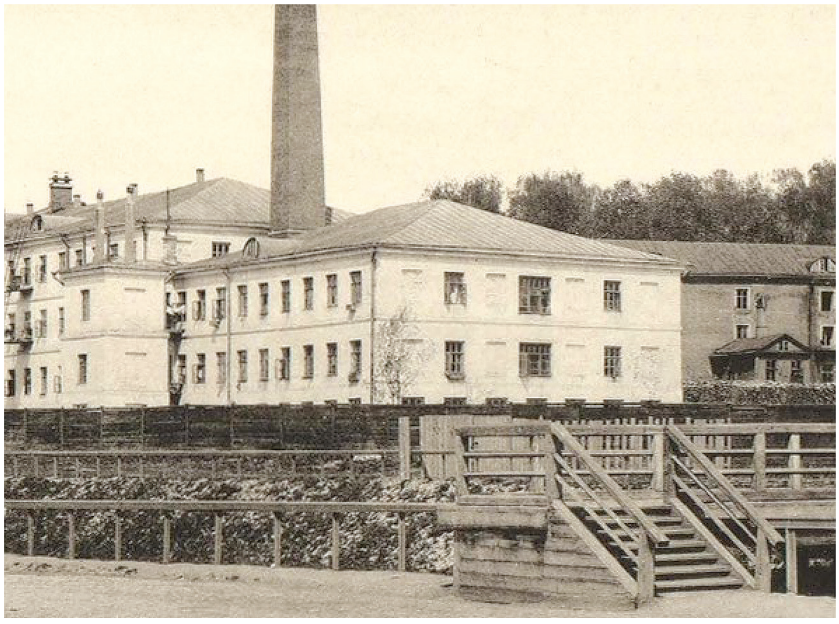

Figure 3. Kotov factory. Photo of the beginning of the 20th century.

and in the evening a banquet for 200 guests was held at the Kotov's cottage located in a picturesque setting on the border of the Preobrazhenskaya and Sokolnicheskaya groves.

In addition to the concert, the highlight of the "cultural program" was the exhibition, for which N. N. Bazhenov selected not only everyday objects from psychiatric hospitals of different centuries (straitjacket, restraint chair, and "case sheets"), but also the creative works of patients (paintings and caricatures, wood and paper crafts, embroidery, and knitting). The models of Preobrazhenskaya Hospital and the Eiffel Tower were particularly popular with the public, because of their size and resemblance to the originals.

In addition to the gala dinner, the guests were treated to a theatrical performance, which included an act from the play "The Marriage of Krechinsky", with a reference to Preobrazhenskaya Hospital, and, at the end of the evening, fireworks from an area near the buildings in Kotov's Half — N. N. Bazhenov did not miss a single opportunity to draw the attention of the patrons and city authorities to the matter of financing the future construction. In 1910–1914, his work culminated in the successful completion of three new buildings and repairs to the old factory facilities on Kotov's Half.

But let's take a closer look at the year of this anniversary: Why was it celebrated in 1909? For a long time, 1809 was mistakenly considered the year in which the first specialized hospital for the mentally ill was opened. It was mentioned both in the Historical Essay on the Imperial St. Catherine's Almshouse by V. Molnar [13] and in the Historical Essay on Preobrazhenskaya Hospital by I. V. Konstantinovsky [9]. For this reason, the anniversary was celebrated in 1909 and the following plaque was installed on the facade of the building: "1809–1909: To the centenary of the Preobrazhenskaya Mental Hospital, the first in Moscow designed specifically for psychiatric purposes".

Only later, while working on the manuscript of his book "The Moscow Dolgauz" or "Essays on the History of Preobrazhenskaya Hospital" did N. N. Bazhenov study the documents in the hospital archives and found out that the new mental health hospital in Preobrazhenskoye was opened earlier, in June 1808, when 53 patients from the house of the former Secret Expedition were transferred to the building on Matrosskaya Tishina[1] [10].

[1] The house on Myasnitskaya Street, formerly owned by the Secret Expedition, was transferred to the Public Charity Office in the early 19th century. This is where the patients of the House of Invalids and the Madhouse were accommodated in 1801.

By the beginning of the 20th century, the records had cemented all three major milestones in the history of the establishment of Preobrazhenskaya Hospital: 1777, 1808, and 1838. One might think that this would have settled the question of the first dates for future celebrations once and for all.

However, the revolution of 1917 and the subsequent division of the hospitals sowed confusion into the "question of anniversaries". In the spirit of Soviet traditions, Preobrazhenskaya Hospital was stripped of its former name in 1920 and became Moscow City Hospital No. 1. What's more, in 1931, it was divided into two independent medical institutions with different goals and missions. The hospitals kept changing names, numbers, internal organizational structure, and overall scope of activities, and only relatively recently, in 2017, did the two hospitals return to their historical roots by merging under the name of P.B. Gannushkin Mental-health Clinic No. 4 (Figure 4).

Over the next 100 years, Kotov's half of Preobrazhenskaya Hospital acquired a different, but equally illustrious, name — Gannushkin Hospital. In the second half of the 20th century, it maintained its position as an advanced center of research and practice, with many pioneering milestones in the history of Russian psychiatry:

- It developed the system of maintenance therapy, which is so important in preventing relapses.
- For the first time in the USSR, it began to use insulin shock therapy (under the direction of M. Y. Sereisky), as well as electroconvulsive therapy (with the contribution of G. A. Rotshtein).
- It also marked the beginning of the "psychopharmacological treatment era in psychiatry" with the trials of many medications that were subsequently integrated into mainstream clinical practice.

RECENT DEVELOPMENTS

Reflecting on the title of this article, "Celebrating a Storied History", one may note that in 2022 the institution historically known as Preobrazhenskaya Hospital will celebrate its anniversary for the first time in more than a century since that memorable evening organized by N. N. Bazhenov at the former Kotov estate. How does Gannushkin Hospital, the illustrious heir

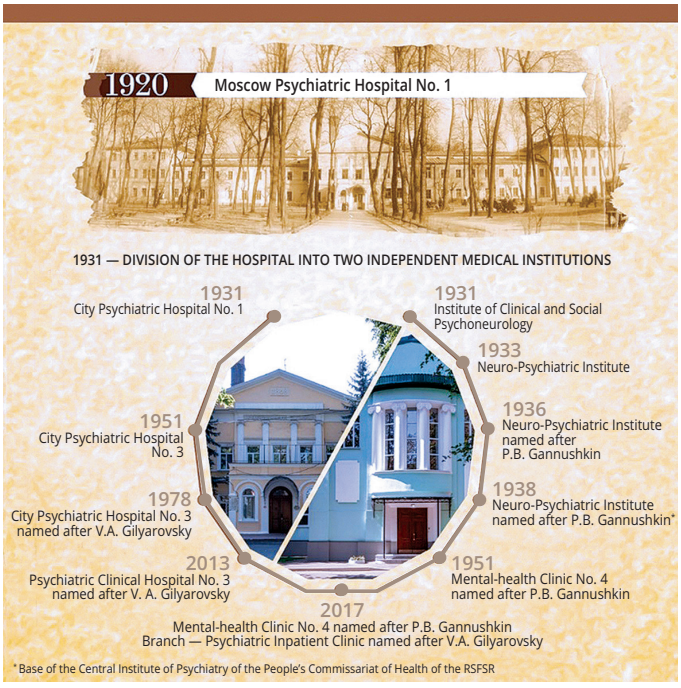

Figure 4. The history of the renaming of the hospital in the 20th century.

to the great traditions established by Preobrazhenskaya Hospital, look at the new generation in the year of its 245th anniversary?

More recently, just 3–4 years ago, it got a facelift after extensive repair and construction work to restore the buildings dating back to the early 20th century. Most importantly, the reorganization allowed for more streamlined psychiatric care, created a common information space, rationalized territorial localization, and brought patient treatment and routing patterns into a consolidated format.

With four specialized clinics in operation since 2020, the hospital now has several new structural units, including a clinic for affective and suicidal disorders, a clinic for borderline conditions, a clinic for first psychotic episodes, a clinic for pharmacoresistant conditions, and a clinic for mental disorders that are compounded by substance abuse. The Mental Health Counseling Center, opened in 2021, provides outpatient care for individuals suffering from various mental disorders including somatoform, stress-related, and neurotic disorders.

Today Gannushkin Hospital boasts a center for complex diagnostics, a clinical and diagnostic department with specialized clinics (such as dentistry, ophthalmology, gynecology, ENT, ultrasound), an anesthesiology and intensive care unit, a clinical and diagnostic laboratory, a psychological and psychotherapeutic center, a social and legal assistance center, as well as a physiotherapy department (including a transcranial magnetic stimulation room and xenon therapy room), pharmacy, X-ray rooms, and a physiotherapy room.

At the moment, the hospital has 9 outpatient branches known as Psychoneurological Dispensaries (PNDs), some of which have a history spanning more than 100 years.[2] Three Memory Clinics were founded on the basis of PND. These medical and rehabilitation units are designed to help elderly patients with early signs of dementia and mild cognitive decline.

The staff of the oldest psychiatric hospital in Moscow has carefully passed down to younger generations traditions that combine the utmost sense of humanity and the highest level of professionalism in helping patients with mental disorders. These traditions are the cornerstone that enables the team at Mental-health Clinic No. 4 named after P. B. Gannushkin to live its mission every day by providing personalized and comprehensive mental health care based on the principles of partnership and trust, with the aim of restoring and maintaining a high quality of life for its patients.

[2] PND No. 8, for example, was founded in 1919 and made psychiatric history as the prototype of the emerging district-level psychiatric care in Soviet Russia.

Article history:
Submitted: 14.02.2023
Accepted: 27.02.2023
Published Online: 23.03.2023

Authors' contribution: All the authors made a significant contribution to the article.

Funding: The research was carried out without additional funding.

Conflict of interest: The authors declare no conflicts of interest.

Supplementary data
Supplementary material related to this article can be found in the online version at doi: 10.17816/CP3704

For citation:
Burygina LA, Golubev SA, Filipchenko OV. Celebrating a storied history: Moscow Preobrazhenskaya mental hospital marks its 245th anniversary. Consortium Psychiatricum. 2023; 4(1):CP3704. doi: 10.17816/CP3704

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