Treatment Advocacy Center

OFFICE OF RESEARCH AND PUBLIC AFFAIRS

Research Summary

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Duration Of Untreated Psychosis: Impact On Brain Health and Psychosis Symptoms

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Duration of untreated psychosis is defined as the time from an individual's first psychotic symptom to the beginning of adequate treatment.[1] In the United States, the median DUP is almost one and a half years, or approximately 74 weeks.[2] This lengthy period of untreated psychosis can potentially have long-lasting health effects.

For decades, researchers have investigated whether long DUP has a toxic effect on neurological and psychological well-being and whether longer DUP is associated with worse social or treatment outcomes.

74 WEEKS **is the average duration of untreated psychois in the U.S.**

This long period of untreted psychosis has many negative effects, including the following:

- **Treatment response worsens.**
- **Insight is lower.**
- **Severity of symptoms increases.**
- **Neurotoxity occurs in the brain.**

Early detection and treatment can reduce these adverse effects and give individuals with psychosis a better chance at recovery.

Structural brain health: Neurotoxicity

Much of the research reporting on the effects of long DUP focuses on the correlation between DUP and neurotoxicity — examining the theory that prolonged or repeated episodes of psychosis leave scars on the brain that cause changes in brain structure, chemical compounds, or neuronal connections.[3] For example, studies have found that long DUP is associated with the following negative effects:

- Temporal and occipitotemporal gray matter volume,[4] which plays a significant role in daily functioning, physical movement, memory, and emotions,[5] is reduced.
- Surface area in the salience and executive networks of the brain is reduced, and cortical thickness increases, all of which cause reduced functioning.[6]
- The brain registers higher levels of fatty acid amide hydrolase,[7] which affects the brain's ability to register feelings of pain and fear.[8]

Morphological changes in the brain may also be associated with the type of illness onset. For example, people with an insidious onset — meaning that the disease does not have obvious symptoms at first[9] —may be more likely to have structural abnormalities due to long DUP.[10]

Neurotoxicity after first-episode psychosis

Although much of the research on DUP explores the potential for neurotoxicity during the first episode of psychosis, evidence suggests that untreated relapses of psychosis occurring after the initial clinical presentation of symptoms can also have a toxic effect on the brain. One study using structural MRI scans and cognitive testing found that long periods of relapse were significantly associated with tissue loss in the brain, including a decrease in total cerebral volume, frontal lobe white matter volume, and temporal lobe white matter volume.[11] Researchers found that the duration of relapse impacted the extent of neurotoxicity, whereas the number of relapses did not.[12]

How long DUP causes neurotoxicity

Two studies included in a 2014 literature review[13] found that the neurotoxic effect of long DUP was caused by dopaminergic hyperactivity, or the prolonged elevation of dopamine, a naturally occurring chemical in the brain that is responsible for feelings of pleasure. Dopamine hyperactivity during a psychotic episode is thought to cause a progressive decline in the volume of certain brain structures.[14] These studies suggest that neurotoxicity is caused by oxidative injury that arises from persistent neurotransmission activities, such as high dopamine and adrenaline levels during psychotic episodes. Similarly, another study argues that structural changes in the brain are caused by the inability to regulate dopamine release and prolonged overstimulation during psychotic episodes.[15]

Social functioning and psychological outcomes

Research has shown that in addition to its adverse effects on structural brain health, long DUP can have a negative impact on social functioning and worsen psychosis symptoms. More specifically, studies have found that long DUP is associated with the following negative outcomes:

- The likelihood of comorbid substance use increases.
- Positive symptoms of psychosis, such as hallucinations and delusions, increase.[16]
- Negative symptoms of psychosis, such as social withdrawal, increase.
- Insight is lower.[17]
- Global functioning decreases (although this associated effect is considered to be relatively small).[18]

A meta-analysis of data from 26 studies also found statistically significant correlations between long DUP (measured at 12 months) and all of the study's measured outcomes, including the following:

- Depression/anxiety.
- Disorganized symptoms (which include incoherent speech patterns, difficulty performing daily activities, and inappropriate emotional response).[19]
- Negative and positive symptoms of schizophrenia.
- Overall functioning.
- Quality of life.
- Social functioning.

Impact on treatment effectiveness

Research also shows that long DUP has a negative association with treatment effectiveness. One meta-analysis found long DUP to be a predictor of poor treatment response,[20] and another study found that the longer the DUP, the worse the treatment response.[21] Researchers suggest that this association is the consequence of the worsened brain

network connectivity that results from long DUP.[22] This research implies that earlier intervention might reduce the negative effect of long periods of untreated psychosis on brain health, thus leading to better treatment outcomes.

Conflicting studies

Not all researchers agree that long DUP has an impact on neurotoxicity or social functioning. A 2014 literature review concluded that there is limited evidence of a relationship between DUP and changes in brain structure or neurocognitive functioning; the researchers found that the majority of the studies observed in the review did not support the hypothesis that long DUP causes neurotoxicity.[23] For example, a 2019 study from Switzerland found no significant relationship between DUP and changes in brain volume after adjusting for age and sex.[24] With regard to social outcomes, a 2020 meta-analysis from the U.K. found that long DUP had no effect on employment, quality of life, or effectiveness of hospital treatment and concluded that any assumed association between long DUP and poor life and treatment outcomes might actually be the result of other factors, such as having good or bad coping mechanisms for psychosis symptoms.[25]

However, some researchers have offered possible explanations as to why these studies do not find a clear association. For example, one group of researchers claimed that studies that have not found evidence of an association between long DUP and structural brain abnormalities tend to have small sample sizes or include patients who have already been exposed to antipsychotics, which skews results.[26]

Another group of researchers who found significant evidence that DUP is inversely correlated with brain function believe that commonly used methodological tools are not capable of accurately examining the effects of long DUP on the brain; these researchers suggest that newer methodologies, such as MRI scanners with stronger magnets and PET imaging, which many of the studies included in this summary used, are much better at capturing these brain processes.[27]

Benefits of early intervention

The majority of relevant research displays convincing evidence that long DUP is correlated with adverse structural brain health and negative psychological and social outcomes. These findings support the case for early treatment intervention programs aimed at reducing the length of untreated psychosis and thereby its impact. Some researchers have found that early intervention has mild positive effects on long-term outcomes for people with schizophrenia. For example, one study with a 10-year follow-up period found that early detection of psychosis was associated with higher recovery rates and improved employment outcomes.[28] Therefore, early detection and treatment interventions have the potential to reduce the adverse effects of long periods of untreated psychosis and give individuals with psychosis a better chance at recovery.

REFERENCES

[1] Marshall, M., Lewis, S., & Lockwood, A. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: A systemic review. *Archives of General Psychiatry, 62*(9), 975–983. https://doi.org/10.1001/archpsyc.62.9.975

[2] Kraguljac, N. V., Anthony, T., Morgan, C. J., Jindal, R. D., Burger, M. S., & Lahti, A. C. (2021, September 26). White matter integrity, duration of untreated psychosis, and antipsychotic treatment response in medication-naïve first episode psychosis patients. *Journal of Molecular Psychiatry, 26*(9), 5347–5356. https://doi.org/10.1038/s41380-020-0765-x; Kane, J. M., Robinson, D. G., Schooler, N. R., Mueser, K. T., Penn, D. L., Rosenheck, R. A., Addington, J., Brunette, M. F., Correll, C. U., Estroff, S. E., Marcy, P., Robinson, J., Meyer-Kalos, P. S., Gottlieb, J. D., Glynn, S. M., Lynde, D. W., Pipes, R., Kurian, B. T., Miller, A. L., … Heinssen, R. K. (2016). Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. *American Journal of Psychiatry*, *173*(4), 362–372. https://doi.org/10.1176/appi.ajp.2015.15050632

[3] Anderson, K. K., Voineskos, A., Mulsant, B. H., George, T.P., & McKenzie, K. J. (2014). The role of untreated psychosis in neurodegeneration: A review of hypothesized mechanisms of neurotoxicity in first-episode psychosis. *Canadian Journal of Psychiatry, 59*(10), 513–517. https://doi.org/10.1177/070674371405901003

[4] Guo, X., Li, J., Wei, Q., Fan, X., Kennedy, D. N., Shen, Y., Chen, H., & Zhao, J. (2013). Duration of untreated psychosis is associated with temporal and occipitotemporal gray matter volume decrease in treatment naive schizophrenia. *PLoS One, 8*(12), e83679. https://doi.org/10.1371/journal.pone.0083679

[5] Mercadante, A. A., & Tadi, P. (2022, July 25). *Neuroanatomy, gray matter.* StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK553239/

[6] Maximo, J. O., Nelson, E. A., Armstrong, W. P., Kraguljac, N. V., & Lahti, A. C. (2021). Duration of untreated psychosis correlates with brain connectivity and morphology in medication-naïve patients with first episode psychosis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 5*(2), 231–238. https://doi.org/10.1016/j.bpsc.2019.10.014

[7] Zoghbi, A. W., Lieberman, J. A., & Girgis, R. R. (2022). The neurobiology of duration of untreated psychosis: A comprehensive review. *Molecular Psychiatry, 28*, 168–190. https://www.nature.com/articles/s41380-022-01718-0

[8] Mayo, L. M., Asratian, A., Lindé, J., Morena, M., Haataja, R., Hammar, V., Augier, G., Hill, M. N., & Heilig, M. (2020). Elevated anandamide, enhanced recall of fear extinction, and attenuated stress responses following inhibition of fatty acid amide hydrolase: A randomized, controlled experimental medicine trial. *Biological Psychiatry, 87*(6), 538–547. https://doi.org/10.1016/j.biopsych.2019.07.034

[9] National Library of Medicine. (n.d.). Insidious. In *A.D.A.M. Medical Encyclopedia*. Retrieved April 22, 2023, from https://medlineplus.gov/ency/article/002382.htm#:~:text=An%20insidious%20disease%20is%20any,not%20aware%20of%20it%20developing

[10] Andreasen, N. C., Liu, D., Ziebell, S., Vora, A., & Ho, B. C. (2013). Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: A prospective longitudinal MRI study. *American Journal of Psychiatry, 170*(6), 609–615.

[11] Andreasen et al. Relapse duration, treatment intensity, and brain tissue loss.

[12] Andreasen et al. Relapse duration, treatment intensity, and brain tissue loss.

[13] Andreasen et al. Relapse duration, treatment intensity, and brain tissue loss.

[14] Crespo-Facorro, B., Roiz-Santiáñez, R., Pelayo-Terán, J. M., González-Blanch, C., Pérez-Iglesias, R., Gutiérrez, A., Marco de Lucas, E., Tordesillas, D., & Vázquez-Barquero, J. L. (2007). Caudate nucleus volume and its clinical and cognitive correlation in first episode schizophrenia. *Schizophrenia Research, 91*(1–3), 87–96. https://doi.org/10.1016/j.schres.2006.12.015; Keshavan, M. S., Haas, G. L., Aguilar, E., Dick, E. E., Schooler, N. R., Sweeney, J. A., & Pettegrew, J. W. (1998). Superior temporal gyrus and the course of early schizophrenia: Progressive, static, or reversible? *Journal of Psychiatric Research, 32*(3–4), 161–167. https://doi.org/10.1016/s0022-3956(97)00038-1

[15] Sheitman, B. B., & Lieberman, J. A. (1998). The natural history and pathophysiology of treatment resistant schizophrenia. *Journal of Psychiatric Research, 32*(3–4), 143–150. https://doi.org/10.1016/S0022-3956(97)00052-6

[16] Addington, J., Heinssen, R. K., Robinson, D. G., Schooler, N. R., Marcy, P., Brunette, M. F., Correll, C. U., Estroff, S., Mueser, K. T., Penn, D., Robinson, J. A., Rosenheck, R. A., Azrin, S. T., Goldstein, A. B., Severe, J., & Kane, J. M. (2015). Duration of untreated psychosis in community treatment settings in the United States. *Psychiatric Services, 66*(7), 753–756. https:///doi.org/10.1176/appi.ps.201400124

[17] Compton, M. T., Gordon, T. L., Goulding, S. M., Esterberg, M. L., Carter, T., Leiner, A. S., Weiss, P. S., Druss, B. G., Walker, E. F., & Kaslow, N. J. (2011). Patient-level predictors and clinical correlates of duration of untreated psychosis among hospitalized first-episode patients. *Journal of Clinical Psychiatry, 72*(2), 225–232. https://doi.org/10.4088/jcp.09m05704yel

[18] Penttilä, M., Jääskeläinen, E., Hirvonen, N., Isohanni, M., & Miettunen, J. (2014). Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: Systematic review and meta-analysis. *British Journal of Psychiatry, 205*(2), 88–94. https://doi.org/10.1192/bjp.bp.113.127753

[19] Ferguson, S. (2021, December 16). What is disorganized schizophrenia? PsychCentral. https://psychcentral.com/schizophrenia/disorganized-schizophrenia#hebephrenic-schizophrenia

[20] Rubio, J. M., & Correll, C. U. (2017). Duration and relevance of untreated psychiatric disorders, 1: Psychotic
disorders. *Journal of Clinical Psychiatry, 78*(3), 358–359. https://doi.org/10.4088/jcp.17ac11479

[21] Maximo et al. Duration of untreated psychosis correlates with brain connectivity.

[22] Maximo et al. Duration of untreated psychosis correlates with brain connectivity.

[23] Rund, B. (2014). Does active psychosis cause neurobiological pathology? A critical review of the neurotoxicity hypothesis. *Psychological Medicine, 44*(8), 1577–1590. https://doi.org/10.1017/S0033291713002341

[24] Rapp, C., Canela, C., Studerus, E., Walter, A., Aston, J., Borgwardt, S., & Riecher-Rössler, A. (2017). Duration of untreated psychosis/illness and brain volume changes in early psychosis. *Psychiatry Research, 255*, 332–337. https://doi.org/10.1016/j.psychres.2017.06.004

[25] Penttilä et al. Duration of untreated psychosis as predictor.

[26] Anderson et al. The role of untreated psychosis in neurodegeneration.

[27] Zoghbi et al. The neurobiology of duration of untreated psychosis.

[28] Hegelstad, W. T., Larsen, T. K., Auestad, B., Evensen, J., Haahr, U., Joa, I., Johannesen, J. O., Langeveld, J., Melle, I., Opjordsmoen, S., Rossberg, J. I., Rund, B. R., Simonsen, E., Sundet, K., Vaglum, P., Friis, S., & McGlashan, T. (2012). Long-term follow-up of the TIPS early detection in psychosis study: Effects on 10-year outcome. *American Journal of Psychiatry, 169*(4), 374–380. https://doi.org/10.1176/appi.ajp.2011.11030459