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Quasi-Experimental Study On Tachyphylaxis In Psychiatric Patients

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Abstract: *The objective of the present ex-post facto study is to the prevalence of tachyphylaxis in patients using psychotropic drugs. Method: As a quasi-experimental style of study, 100 participants were purposively selected who were admitted to the rehabilitation centre for the treatment of substance-induced disorders, Psychotic disorders, Bipolar disorder and other psychiatric disorders and being treated with medication. The age range was 18 to 60 years. An Urdu-translated version of the Rothschild Scale for Antidepressant Tachyphylaxis (RSAT) was used to find out the prevalence of tachyphylaxis in patients. Results: A significant number of patients were found with tachyphylaxis after treatment of 6 or more than six months as they were being treated with antipsychotics, antidepressants, anxiolytics, tranquillizers and narcotics.*

Key Words: Tachyphylaxis, Rothschild Scale for Antidepressant Tachyphylaxis (RSAT), Anti-Psychotic medication

Introduction

Tachyphylaxis, a term derived from Greek roots meaning "rapid protection," is commonly defined as "increased tolerance to a drug that develops after continuous or repeated exposure to that drug" (Lieb and Balter, 1984; Solomon, 2005). In the context of antidepressant therapy, it refers to the phenomenon where a depressed patient, despite continuing with the same medication and dosage for maintenance therapy, experiences a loss of the positive antidepressant treatment response that had previously been observed.

There is, however, a degree of ambiguity surrounding the terminology used to describe this phenomenon, with "antidepressant tachyphylaxis," "poop-out," and "tolerance" sometimes used interchangeably. While some studies suggest that tachyphylaxis might be associated with habituation or sensitization mechanisms, others argue that it could be due to factors such as non-adherence to treatment (Targum, 2014).

Research has shown that individuals with depression who experience "true" antidepressant tachyphylaxis may become less responsive to conventional therapeutic approaches. For instance, a study by Amsterdam et al. (2009) found that the initial response to sertraline therapy was inversely correlated with the number of prior antidepressant drug exposures, suggesting that repeated exposure to antidepressants could lead to tachyphylaxis.

Tachyphylaxis isn't limited to antidepressants; it has also been observed in individuals with chronic schizophrenia undergoing

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antipsychotic treatment. However, some studies have suggested that aripiprazole may not lead to tachyphylaxis (Goto et al., 2012). Additionally, the dose-response relationship for antipsychotic drugs can change with age, with the potential for tachyphylaxis developing after multiple trials of antidepressant medications (Uchida and Mamo, 2009).

It's essential to distinguish between tachyphylaxis and other terms like relapse and recurrence in the context of depression. Recurrence, for example, refers to a subsequent depressive episode that occurs after at least six months, while tachyphylaxis typically requires ongoing treatment to be diagnosed. Therefore, precise terminology and understanding are crucial in this field (Targum, 2014).

In conclusion, tachyphylaxis in the context of antidepressant therapy is a complex phenomenon associated with a reduced response to medication over time. While its exact mechanisms and causes are still under investigation, it is clear that this phenomenon poses challenges in the treatment of depression and highlights the need for personalized treatment approaches.

Tachyphylaxis, originally meaning "rapid protection," is currently defined as "increased tolerance to a drug that arises with continuous or repeated exposure to that drug" (Lieb and Balter, 1984; Solomon, 2005). In a series of publications between 1968 and 1970, Cohen, Bromage, and Spoerel explored the emergence of resistance to the effects of local and epidural anaesthetics.

Antidepressant tachyphylaxis refers to a situation in which a depressed patient, undergoing maintenance therapy with the same medication and dosage, experiences a loss of the previously beneficial antidepressant treatment response. It's important to note that factors other than tolerance, such as non-adherence to treatment, can also contribute to this loss of therapeutic response. While antidepressant tachyphylaxis is associated with developing medication tolerance, studies have suggested that individuals experiencing "true" antidepressant tachyphylaxis may become less responsive to innovative therapy strategies. Hence, it is essential to recognize such patients as part of comprehensive treatment planning (Targum, 2014).

Literature Review

A significant number of individuals experience recurrent major depression despite being on maintenance medication. To improve prevention in such cases, it is crucial to develop alternative treatment plans based on a deeper understanding of recurrence (Solomon et al., 2005).

In a study, researchers investigated whether antidepressant tachyphylaxis develops with repeated medication use. The study revealed an adverse correlation between the initial response to sertraline therapy and the number of previous exposures to antidepressant drugs (odds ratio = 0.81, p = 0.0035). The odds ratio indicates that with each prior antidepressant trial, the likelihood of responding decreases by 19.9%. However, there was no observed relationship between the number of previous antidepressant treatment attempts and the response to continued sertraline in combination with atomoxetine or sertraline in combination with a placebo. This data lends support to the notion that repeated trials of antidepressant medication may lead to tachyphylaxis (Amsterdam et al., 2009).

Tachyphylaxis poses a significant therapeutic challenge for individuals with chronic schizophrenia, involving a loss of antipsychotic efficacy that may be attributed to an increase in D2 receptor quantity and sensitivity. However, animal research suggests that aripiprazole may not induce tachyphylaxis. To investigate this theory, a recent pilot study retrospectively examined tachyphylaxis in individuals receiving aripiprazole. The study found no significant changes in Clinical Global impression improvement (CGI-I) scores, and there was no correlation between CGI scores and the duration of fixed dosage. These findings suggest that aripiprazole may not be associated with tachyphylaxis (Goto et al., 2012).

Uchida and Mamo (2009) reported that the dose of antipsychotic medication increased with age, plateaued, and then decreased after the fifth

decade. The first half of this inverted U-shaped association can be attributed to a reduction in the early phases of schizophrenia and the development of "tachyphylaxis" in response to antipsychotic drugs affecting the dopaminergic system. This observation supports the possibility of tachyphylaxis developing after multiple trials of antidepressant medication (Amsterdam et al., 2009).

Several intriguing characteristics of SSRIs include the inability to predict a patient's treatment response, inter-individual variations in side effects, and the phenomenon of tachyphylaxis, which involves a rapid loss of medication responsiveness. Additionally, there are still unanswered questions regarding how SSRIs exert their clinical effects. SSRIs affect enteric neurons, which are responsible for producing the majority of serotonin in the human body. Furthermore, SSRIs possess antibacterial properties that may impact microbial balance (Sjöstedt, Enander, & Isung, 2021).

Antidepressant tachyphylaxis refers to the situation where a depressed patient, while maintaining the same medication and dosage for therapy, no longer experiences the positive response to antidepressant treatment that was previously observed. It's important to note that factors unrelated to tolerance, such as non-adherence to therapy, may also contribute to the loss of therapeutic response. Drug tolerance is often considered the underlying cause of antidepressant tachyphylaxis, which represents a specific form of recurrence. Several studies have indicated that individuals with depression who experience "true" antidepressant tachyphylaxis may become less responsive to conventional therapy approaches (Skaff, 2019).

In 1984, Lieb and Balter described tachyphylaxis to antidepressants, lithium, or ECT in eleven patients. These individuals represent a small subset of those who did not sustain a positive initial response to mood-regulating medications. Further comprehensive research may reveal that tachyphylaxis is a common outcome of antidepressant therapy.

As described by Katz (2011), tachyphylaxis refers to the progressive reduction in reactivity to a dose following repeated administration of a pharmacologically or physiologically active substance. These symptoms may also manifest after antidepressant therapy.

Although the exact prevalence of the condition is unknown, pharmacological treatment of depression has been demonstrated to reduce its severity by up to 33%. The review discusses potential causes and treatments for tachyphylaxis following antidepressant therapy. Among the study participants, twelve patients (23%) and thirteen trials (22.4%) experienced occurrences of tolerance or tachyphylaxis, respectively. Notably, every patient receiving a single therapy eventually developed tolerance. Tachyphylaxis did not manifest in the non-SSRI group, while 41.9% of successful cases in the SSRI group exhibited tolerance ($P = 0.001$).

Methodology

The objective of this ex-post facto study is to investigate the prevalence of tachyphylaxis in patients using psychotropic drugs.

An ex post facto design is categorized as a quasi-experimental research approach, where participants are grouped based on shared characteristics or attributes rather than being randomly assigned. Ex post facto research examines how past events can serve as predictors of future outcomes.

Sample

In this quasi-experimental study, we purposively selected 50 patients who were admitted to a rehabilitation centre for the treatment of substance-induced disorders, psychotic disorders, bipolar disorder, and other psychiatric disorders, all of whom were undergoing treatment with psychotropic medications. The age range of the participants was between 18 and 60 years.

Scale

To determine the prevalence of tachyphylaxis in

patients, we translated the Rothschild Scale for Antidepressant Tachyphylaxis (RSAT) into Urdu. The RSAT, developed by Rothschild, includes one clinician-rated item for effect and six self-report items assessing energy levels, motivation, interest, cognitive functioning, weight gain, sleep patterns, and sexual functioning (Rothschild, 2008). We used the entire RSAT instrument and identified tachyphylaxis when at least one of the following symptoms—apathy or reduced motivation, fatigue, cognitive dullness, sleep disturbances, weight gain, and sexual dysfunction—persisted for a minimum of two weeks after the antidepressants had been fully effective for at least three months.

The Rothschild Scale for Antidepressant Tachyphylaxis (RSAT) was employed to evaluate the seven symptoms associated with tachyphylaxis, including drive and interest, cognitive function, weight gain, sleep problems, and sexual performance.

Null Hypothesis H_0

Tachyphylaxis does not occur in patients taking antipsychotic medications for a long time.
Tachyphylaxis does not occur in the patients taking antidepressant medications for a long time.
Tachyphylaxis does not occur in the patients taking anxiolytic medications for a long time.
Tachyphylaxis does not occur in patients taking tranquillizer medications for a long time.
Tachyphylaxis does not occur in the patients taking narcotics for a long time.

Results

Table 1

Tachyphylaxis occurred in patients (N=100) taking antidepressants (n=20), Anti-Psychotic (n=20), Anxiolytics (n=20), Tranquilizers (n=20) and Narcotics (n=20) respectively (P .02), due to a greater prevalence of tachyphylaxis.

	Anti-Depressant (n = 20)	Anti-Psychotics (n = 20)	Anxiolytics (n= 20)	Tranquilizers (n=20)	Narcotics (n=20)
Age (years), mean (SD)	42.0 (10.4)	43.0 (11.7)	42.6 (13.3)	45.0 (43.0)	40.1 (41.2)
Weight (lb), mean (SD)	178.8 (46.3)	185.9 (50.0)	185.9 (49.7)	180.5 (47.0)	186.2 (44.5)
Height (in), mean (SD)	66.8 (3.7)	66.9 (3.8)	66.1 (3.5)	66.0 (3.6)	66.5 (3.9)
BMI, mean (SD)	28.1 (6.4)	29.1 (7.1)	29.9 (7.6)	29.5 (6.5)	28.5 (6.0)
Duration of taking medicine in years), mean (SD)	6.3 (6.3)	7.9 (6.8)	7.1 (5.9)	7.5 (6.5)	7.3 (6.1)
RSAT Total Score, mean (SD)[a]	4.8 (4.0)	4.6 (3.5)	4.6 (4.1)	4.7 (4.2)	4.5 (4.1)

Abbreviations: BMI = body mass index; RSAT = Rothschild Scale for Antidepressant Tachyphylaxis; SD = standard deviation

Table 1 shows that there is a significantly high score of patients using antidepressants, antipsychotics, anxiolytics, tranquillizers and narcotics on the scale measuring tachyphylaxis. It is also evident that the highest scores are found on the Rothschild Scale for antidepressant

tachyphylaxis in patients who are using tranquillizers and antidepressants.

It is also found that patients taking antipsychotics get medicines for the longest duration which develops tachyphylaxis against medicines. While comparing the scores on the scale of tachyphylaxis the highest score is found in the patients who are on antidepressants. Whereas, there are significantly high scores on this scale in the patients who are taking antipsychotics, anxiolytics, tranquilizers and Narcotics.

Discussion

The primary objective of the present ex-post facto study was to investigate the prevalence of tachyphylaxis in patients using psychotropic drugs. Five null hypotheses were formulated and subsequently rejected, confirming that tachyphylaxis occurs in patients using antipsychotic, antidepressant, anxiolytic tranquillizers, and narcotics medications over extended periods. These findings are consistent with existing literature, particularly in the context of recurrent major depression despite maintenance medication use (Solomon et al., 2005).

A study examined whether antidepressant tachyphylaxis occurs after repeated medication use. The results revealed a negative correlation between the number of prior antidepressant exposures and the initial response to sertraline therapy (odds ratio = 0.81, $p = 0.0035$), indicating that the likelihood of responding decreases by 19.9% with each previous antidepressant trial. However, the response to sertraline in combination with atomoxetine or placebo was not influenced by prior antidepressant trials, supporting the hypothesis that repeated antidepressant use may lead to tachyphylaxis, as suggested by Amsterdam and Shult (2009).

Amsterdam and Shult (2009) identified potential causes of tachyphylaxis, including underlying illness, genetic predisposition for non-response, physiological adaptation with repeated antidepressant use, and pharmacokinetic variability. Tachyphylaxis rates varied from 9% to 57% based on patient demographics and follow-up duration. Limited research suggests that adjusting antidepressant dosages, switching medication classes, combining pharmacotherapy, and incorporating psychotherapy may be beneficial in treating tachyphylaxis (Kinrys et al., 2019).

Katz (2011) defines tachyphylaxis as the diminishing sensitivity to a drug's effects following repeated administration. This phenomenon can also occur during antidepressant therapy, with an estimated prevalence of up to 33%. Katz's review explores potential causes and treatments for tachyphylaxis during antidepressant therapy. Notably, 23% of patients and 22.4% of trials experienced tolerance or tachyphylaxis, with all patients receiving a single treatment eventually developing tolerance. Furthermore, tachyphylaxis was less common in the non-SSRI group compared to the SSRI group.

Conclusion

In conclusion, the present study supports the notion that tachyphylaxis occurs in patients who use antipsychotic, antidepressant, anxiolytic tranquillizers, and narcotics medications over an extended duration. It is worth noting that while there is substantial literature on tachyphylaxis in the context of antidepressant use, there is a dearth of research on tachyphylaxis associated with long-term usage of anxiolytics, antipsychotics, tranquillizers, and narcotics.

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