# Exploring the incidence and etiopathogenesis of pathological yawning as adverse side effect of psychotropic drugs

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**Introduction:** Yawning is a normal, stereotyped physiological event in humans and animal kingdom. When excessive (>3 per 15 minutes), it is termed as pathological yawning (PY). PY could be due to many causes but more commonly associated with side-effect of drugs, notably involving those used in psychopharmacology. Though there are isolated case reports and case-series, there are no large-scale reports of PY. This work attempted to address this lacuna. **Material and Methods:** The current work attempted to identify characteristics of PY as collated from adverse drug effect databases of Australia (Database of Adverse Event Notifications), Canada (Canada Vigilance Adverse Reaction Online Database) and the United States of America (FDA Adverse Event Reporting System - FAERS). These databases collect and provide public access to reports of adverse events related to drugs and therapeutic goods. They act as a prime pharmacovigilance tool as well as a first-line resource for healthcare professionals, researchers, and the public to monitor the safety of these products and make informed decisions. In the first week of June 2023, open access, unrestricted adverse effect of drug databases were explored, using the word "YAWNING" as the only search term for the side effect of any drug without any restrictions. The collected details of PY cases with their gender, age, reason for drug use, other concomitant complaints as well as the nature of adverse event(s) and its treatment requirements were assessed. Descriptive statistics were used. **Result:** Of the 2655 instances in USA database, 398(15%) had more than 1 suspect drug and in total 578 medications involved. The most commonly involved drugs were apomorphine, sertraline, fluoxetine and paroxetine. In all 341(12.8%) cases reported of YAWN alone or with one another sleep disorder, the most common offending drug were fluoxetine hydrochloride. **Discussion and Conclusion:** The neural mechanism and physiology of yawning are explained. This study stresses that a health care professional, particularly mental health professionals and neurologists, should be aware of the importance of PY to deliver the best for the patients under their care.

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**Keywords:** Pathological Yawning, Adverse Drug Reaction, Medications, Psychiatric Medication, Neurological Side Effects, Etiopathogenesis

## INTRODUCTION

Yawning or gaping, or oscitation is a conserved, stereotyped physical behaviour, considered by some as an involuntary reflex, which is found among vertebrates. The act itself is comprised of three stages - a long inspiratory phase with gradual mouth gaping, followed by a brief climax with powerful facial-neck muscle stretching, and a rapid expiratory phase with muscle relaxation. Each yawn lasts about 4-to-7 seconds and on an average, a human foetus yawns about 25/day that decreases to 9(0-28)/day in adult, with each bout of about 2-or-3 act, each with increasing intensity (Doelman & Rijken, 2022). On an average, frequency of spontaneous yawns was 13.46±1.61 times with frequency peaking in the early morning and in the late evening, with wakefulness positively correlating with the time course of sleepiness (Giganti & Zilli, 2011). Also, it is reported to be the most prevalent oral behaviour (activities occurring beyond physiological function of the stomatognathic system) with about 3-in-4 subjects reporting this behaviour (Reda et al., 2023). Several hypothesis including "brain arousal", "respiration", "communication" "brain cooling" and "airway physiology" have been proposed for the exact function of yawning (Rothenberg, 2021).

An abnormal yawning may be associated with diseases or medications. In an emergency room, when repetitive yawning occurs in medically unstable, critically-ill patients, it could be an indicator of mortality and morbidity (Rothenberg, 2021). Yawning is associated during and after cerebrovascular insult, in locked-in syndromes, brain tumours and injuries, epilepsy, migraine, neurodegenerative disease, amyotrophic lateral sclerosis, multiple and extrapyramidal diseases (Krestel et al., 2018). It is also reported in patients with sleep disorders, functional digestive disorders, motion sickness, hypoglycemia in diabetics, vasovagal syncopal or pre-syncopal episodes and depression (Krestel et al., 2018). Drugs that precipitate yawning includes anti-depressants, dopaminergic agents, opioids and benzodiazepine. The selective serotonin reuptake inhibitors (fluoxetine, paroxetine, escitalopram, venlafaxine and duloxetine), dopaminergic drugs (levodopa, pramipexole, ropinirole, rotigotine and apomorphine) and monoamine oxidase inhibitors are the most common drugs that produce yawning as side-effect (Teive et al., 2018).

Yawning is self-limiting, common physiological event and traditionally associated with boredom or insomnia and never popularly or publicly associated as a side-effect or an adverse effect of any drug. Hence due attention is not given and most often, under-reporting of the adverse incidence happens. Though common, the need to understand the pathophysiology of yawning and influence of therapeutic agents on this phenomenon is needed to create better drugs. The literature on occurrence of yawning as an adverse or side effect due to drug administration is rare (Sommet et al., 2007). An attempt was made to qualitatively assess the reporting of yawning as an adverse effect of drugs from open access pharmacovigilance databases from USA, Canada and Australia.

## MATERIAL AND METHOD

This study did not involve human or animal subjects and all available data were collected from resources available in the world wide web and such an approach does not require any ethical clearance.

In the first week of June 2023, the websites of SIDER 4.1 (Side Effect Resource, http://sideeffects.embl.de) was explored for drugs commonly associated with yawning. This website was formulated in 2015 and has 5868 side-effects in 1430 drugs with 139756 drug-side-effects pair. A search was made using "yawning" as the side-effect (Kuhn et al., 2015).

In the first week of June 2023, open access, unrestricted adverse effect of drug databases of Australia (https://daen.tga.gov.au/medicines-search), Canada (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html) and United States of America (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard) were explored, using "YAWNING" as the only search term for the side-effect of any drug without any restrictions. The total number of cases, gender and age distribution, nature of complaints was explored. Pattern of reporting of unusual drugs were also noted. A note was made on the number of cases where yawning was the presenting complaint. Similarly, the cases where yawning along with only one indicator of sleep disorder (dyspnoea, fatigue, headache, hypersomnia, insomnia, lethargy, sedation or somnolence) was noted down. If more than 1 conditions besides yawning was noted, it was categorized as multiple symptoms.

In the same time-frame, Target - Adverse Reaction Database Integrated Search (ARDIS) was launched at http://www.bioinsilico.org/T-ARDIS/ for yawning both in curated and self-reporting format. This

**Table-1.** Reported incidences of yawning due to drugs in SIDER Database version 4.1*

| DRUG | Reported incidence of Yawning as a side effect |
|---|---|
| Apomorphine | 40% |
| Citalopram | 0.7% - 5.3% |
| Clomipramine | 3% |
| Desvenlafaxine | 1% - 4% |
| Duloxetine | 2% |
| Fluoxetine | 1% - 11.1% |
| Fluvoxamine | 0% - 5% |
| Paroxetine | 0% - 5% |
| Ropinirole | 3% |
| Sertraline | Post-marketing, common, frequent |
| Venlafaxine | 3% - 8% |
| Nefazodone; Dihydroergotamine; Deprenyl; Eletriptan; Lamotrigine; Pregabalin; Riluzole; Risperidone; Rizatriptan; Sumatriptan; Zolmitriptan; Zolpidem | Rare/Infrequent/ Uncommon |
| Methadone; Midazolam; Milnacipran; Morphine; Naloxone; Naltrexone; Oxycodone; Pilocarpine; Pramipexole; Sibutramine; Tramadol; Bupropion; Hydromorphone; Labetalol; L-Dmp; Mersyndol; Cevimeline; Clonazepam; Codeine | Has been reported |

*Refer: Kuhn M, Letunic I, Jensen LJ, Bork P. (2015) The SIDER database of drugs and side effects. Nucleic Acids Res. 19; 44(D1):D1075-9

is a searchable database that contains pairwise associations between adverse drug reactions and publicly available gene targets (Galletti et al., 2021). An attempt was made to elucidate the identify the specific gene-disease(s) link from the Disease Gene Network (https://www.disgenet.org/) by employing the tool at https://www.networkanalyst.ca/. An attempt was also made to study the gene-drug interaction at hippocampus level using the http://stitch.embl.de/ tool.

## RESULTS

The cumulative results of the SIDER database are depicted in Table-1. The common drugs involved belong to anti-depressants, dopaminergic agents, opioids and benzodiazepine group. Yawning associated with other group of drugs are extremely rare events.

In the Australian database, between 1/1/1971 to 18/5/2023, 135 cases were reported with no deaths. There were 90 (67%) females and 42 (33%) males. Age distribution was 5 (4%) cases <12 years, 1 in 12-17 years, 91 (67.4%) in 18 to 64 years and 17 (12.6%) in >65 years age group. Interestingly, it came from 51 medicines and in 117 (86.7%) instances, it was due to single medication. Yawing was the only side-effect in 21 (15.5%) cases and yawning with another sleep disorder was the reported effect in 31 (23%) cases. Interestingly 17 (12.6%) cases were associated with vaccines. The COMIRNATY® (Tozinameran) produced yawning in 10 (7.4%) cases, The Oxford/AstraZeneca (ChAdOx1-S recombinant) vaccine in 4 cases, Fluvax®, Infanrix –HEXA® and Infanrix- IPV® – one each case.

In the Canadian database, during the period 1/1/1965 to 31/1/23, there were 108 cases reported with 71 (65.7%) females and 37 (34.3%) males. Of this, poly-pharmacy was observed in 17 (15.7%) instances and 11 (10.2%) cases of yawning alone. Another 4 cases had yawning with sleep disorders.

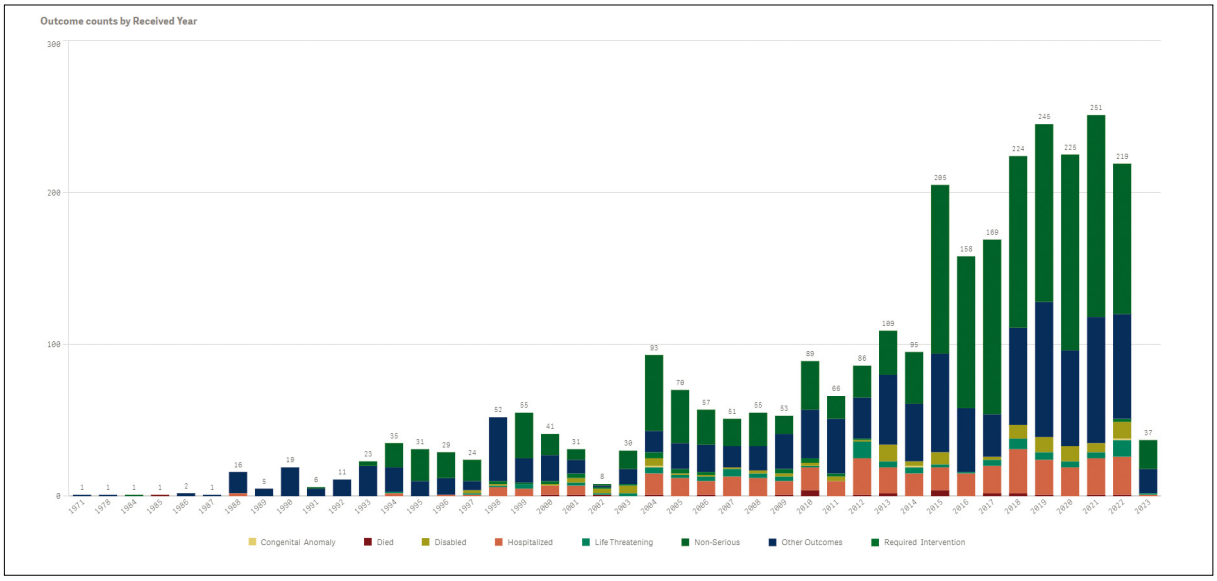
In the USA database, there were 2655 instances of yawning being reported as a side-effect between 1/1/1971 to 31/3/2023. Of this, 1486 (59.9%) were females, 995 (40.1%) males and 174 were not specified. Eighty-two (4.2%) were below 18 years, 1311 (66.5%) between 18 to 64 years, 536 (27.18%) between 65 to 85 years. Age was not mentioned in 683 instances. The mean age was 50.99±19.73 years. Of the 2655 instance, the organization reported that 1291 (48.63%) were serious and 25 of them resulted in death. Of the 2655, 398 (15%) had more than 1 suspect

**Table-2.** Genes associated with yawning as per Target - Adverse Reaction Database Integrated Search (ARDIS)

| Drug name | Curated-Database(s)* | Self-reporting database(s)* |
|---|---|---|
| AMITRIPTYLINE | | ADRA2A; ADRA2C; HTR1A; OPRM1; HTR2C |
| APOMORPHINE | HTR1A; HTR1B; HTR2B; HTR2C | |
| BUPRENORPHINE | | OPRM1 |
| CIPROFLOXACIN | | KCNH2 |
| CITALOPRAM | HTR2C | HTR2C; KCNH2 |
| CLOMIPRAMINE | HTR2B, HTR2C | |
| CYCLOSPORINE | | EDN1; CXCL8 |
| DIHYDROERGOTAMINE | HTR1A; HTR2C; HTR1B; HTR2B; HTR1F | |
| DULOXETINE | HTR2C | |
| ELETRIPTAN | HTR2B; HTR1F; HTR1B; HTR1A | |
| FENTANYL | | CXCL8; OPRM1 |
| FLUOXETINE | HTR1A; HTR2C; HTR2B; HTR1B | HTR2C; KCNH2; CXCL8; EDN1; HTR1A |
| GABAPENTIN | | ADRA2A |
| LABETALOL | | ADRA2C; ADRA2A |
| METFORMIN | | LEP |
| METHADONE | | OPRM1 |
| METHYLPREDNISOLONE | | CXCL8 |
| MILNACIPRAN | HTR1A | |
| MIRTAZAPINE | | DRD2; HTR2C; ADRA2A; HTR1A; ADRA2C; DRD3 |
| NEFAZODONE | HTR2C; HTR1A | |
| NICOTINE | | CXCL8 |
| NIFEDIPINE | | EDN1 |
| NORTRIPTYLINE | | HTR2C; ADRA2A; HTR1A; DRD2 |
| PRAMIPEXOLE | HTR1A; HTR2B; HTR1B; HTR2C | |
| RISPERIDONE | HTR2C; HTR2B; HTR1F; HTR1B; HTR1A | |
| RIZATRIPTAN | HTR1A; HTR1B; HTR1F | |
| ROPINIROLE | HTR2C; HTR2B; HTR1B; HTR1A | |
| SPIRONOLACTONE | | EDN1 |
| SUMATRIPTAN | HTR1A; HTR1B; HTR1F; HTR2C | |
| VITAMIN D | | LEP; CXCL8 |
| VITAMIN D3 | | CXCL8 |
| ZOLMITRIPTAN | HTR1A; HTR1B; HTR1F | |

*Refer: Galletti C, Bota PM, Oliva B, Fernandez-Fuentes N. (2021). Mining drug-target and drug-adverse drug reaction databases to identify target-adverse drug reaction relationships. Database ;20; baab068

**Figure-1.** Bar graph showing the time period and the nature of the side effect as reported in the USA database




drug and in total 578 medications involved. The most commonly involved drugs were apomorphine, Sertraline, Fluoxetine and paroxetine. The patients most commonly suffered from depression spectrum (n=424), Parkinson's (n=373) and anxiety (n=173).

Of the 1291 serious cases, 384 (15%) had to be hospitalized and 69 (2.6%) had morbidities. The Figure-1 shows the incidence and year wise reporting of yawning in the database. The condition seems to be increasingly being reported in the recent years more often than in the past.

Of the 2655 instances, yawning was the first complaint in 708 (26.7%) cases and in 188 (7.1%) cases, it was the only complaint. In all 341 (12.8%) cases reported of yawning alone or with one another sleep disorder. In the 188 cases that had yawning as the only complaint, the most common offending drug were fluoxetine hydrochloride (n=41, 20%) followed by sertraline hydrochloride (n=35, 17.1%) and apomorphine hydrochloride (n=22, 10.7%). In the 341 case that reported of yawning alone with one another sleep disorder, the commonly involved drugs were apomorphine hydrochloride (n=73,19.9%), fluoxetine hydrochloride (n=48,13.1%) and sertraline hydrochloride (n=37,17.1%). The common offending drugs are depicted in graph in Fiugure-2.

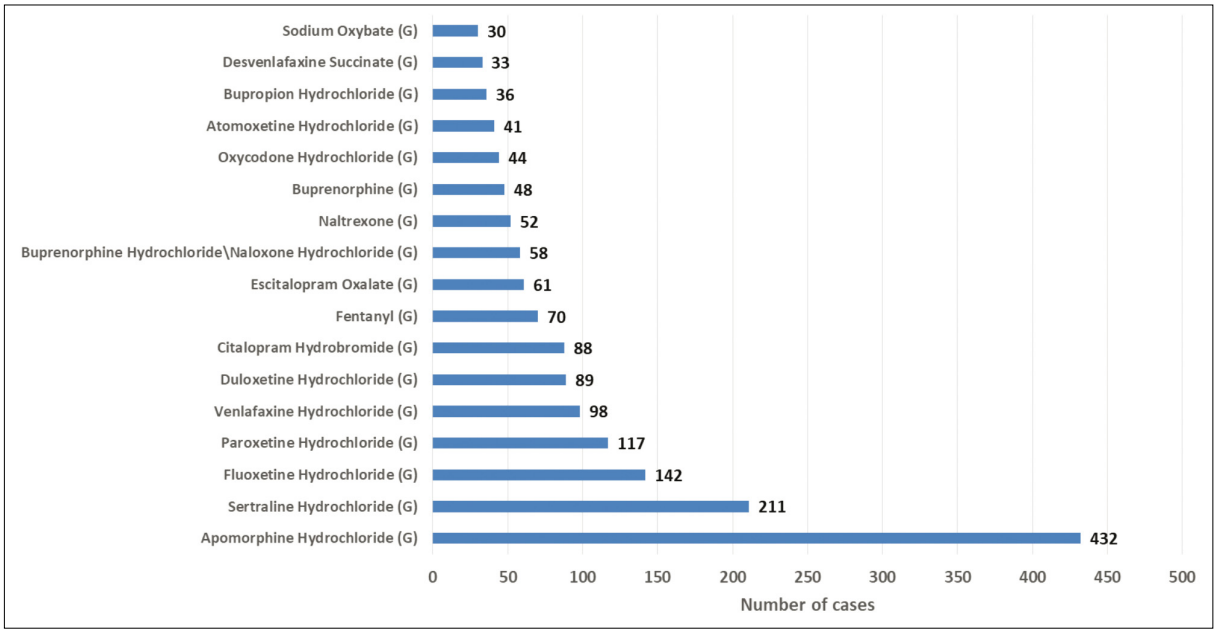
ARDIS website revealed that the genes associated with yawning included ADRA2A, ADRA2C, CXCL8, DRD2, DRD3, EDN1, HTR1A, HTR1B, HTR1F, HTR2B, HTR2C, KCNH2, LEP and OPRM, with the gene depicted in Table-2. The Figure-3 shows the diseases(s)-gene network and the Figure-4 show the possible gene-drug interaction at hippocampus level.

## DISCUSSION

A yawn is believed to be triggered in a low-vigilance state of the brain that is in transition between wake-sleep cycles with both the ends provoking a yawn. It could be endogenous (stressful events, imitation of a yawn, and hungriness) or exogenous [direct or indirect sensory inputs about yawn – "contagious yawning"; Opioid withdrawal syndrome, psychoactive drugs (apomorphine, naloxone), and neurological diseases (amyotrophic lateral sclerosis, multiple sclerosis)]. Certain opioid peptides inhibit yawn while some psychotic disorders decrease yawn. The cut-off value for excessive yawning is fixed at 3-per-15 minutes (Doelman & Rijken, 2022). This act is executed by orchestration of firing of neurons in a particular, rhythmical order, precipitating a complex pattern of contracting muscles around the respiratory and oro-pharynx. The act is initiated in brainstem and closely associated with centres for breathing, swallowing, mastication, and coughing (Doelman & Rijken, 2022). The neural steps involved are showed in Figure-5A.

Animal studies show that the brain centre of yawning is along the pontomedullary central pattern generators. The locus coeruleus and the paraventricular nucleus (PVN) make up the motor system of yawning. PVN is considered to be the supratentorial control area that

**Figure-2.** The drugs that triggered pathological yawning as reported in the USA database

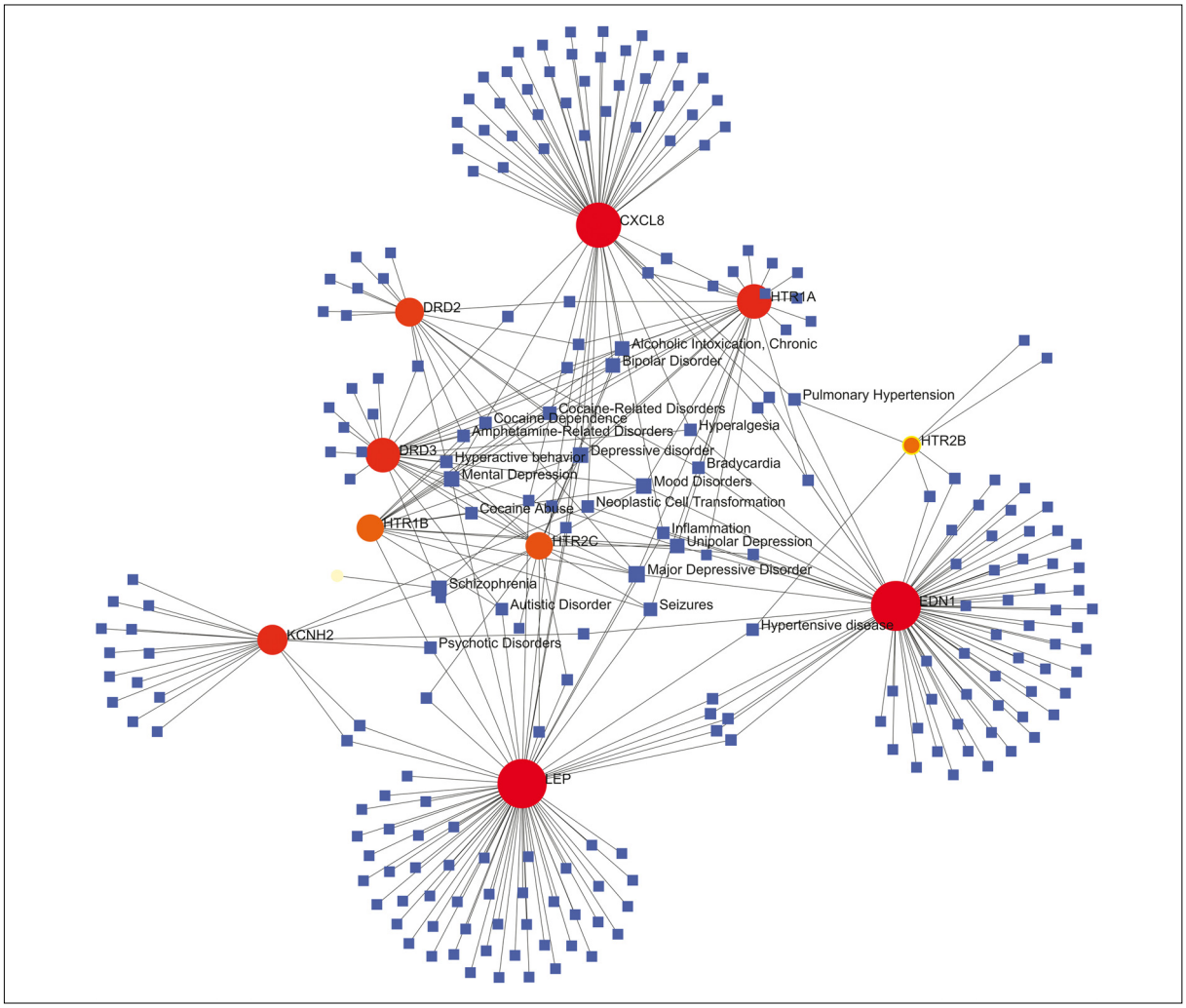



connects the central and peripheral autonomic nerve systems. Oxytocinergic neurons of the PVN project through the medial forebrain bundle to structures in the brainstem that control respiratory, cardiovascular, and autonomic functions. This together with the corticotropin-releasing factor neurons in the PVN are associated with the induction of the yawning that are associated with neural arousal response. The structures like the locus coeruleus, solitary nucleus, ventrolateral medulla, the motor nucleus of the vagal nerve, and other motor nuclei like those of the trigeminal, facial, and hypoglossal nerves control vital, basic human functions. The Pre-Botzinger complex (a group of interneurons in the ventrolateral medulla, that mediates breathing rhythms, send signals to motor nuclei like the phrenic nerve (C1-C4)) that controls the diaphragm (Dourish CT & Cooper SJ, 1990, Krestel et al., 2018).

Yawning uses this whole network of nerve communication. Yawning is triggered by parvocellular oxytocinergic neurons in the PVN that send signals to the lower brainstem. Yawning happens when these neurons are stimulated by dopamine and its agonists, excitatory amino acids (N-methyl-D-aspartic acid), oxytocin itself, or electrical stimulation. On the other hand, yawning ceases when these neurons are blocked by gamma-aminobutyric acid (GABA) and its agonists or by opioid peptides and opiate-like drugs. Nitric oxide synthase is another gaseous neurotransmitter influencer. It makes nitric oxide, which triggers the release of oxytocin in brain places outside of the hypothalamus. In the hippocampus and the reticular structure of the brainstem, oxytocin turns on cholinergic neurotransmission. Acetylcholine triggers yawn by acting on the muscarinic receptors of effectors, which are the respiratory neurons in the medulla, the motor centres of the V$^{th}$, VII$^{th}$, IX$^{th}$, X$^{th}$, and XII$^{th}$ cranial nerves, the phrenic nerves (C1-C4), and the motor supply to the intercostal muscles (Dourish CT & Cooper SJ, 1990, Krestel et al., 2018) (Figure-5A, 5B).

Patient themselves consider yawning arising due to drugs annoying but non-harmful. Lavertu A et al., studied the social media postings of patients to device a "Severity of Adverse Events Derived from Reddit (SAEDR)" score. Based on severity as perceived by the public's social media posting, SAEDR score was allotted. It was high for severe, life-threatening conditions and low for non-severe conditions. General public placed yawning with a score of 0.243±0.09, much closer to injection site paraesthesia and dryness in medication application site (Lavertu et al., 2021). Though a normal physiological phenomenon, its occurrence as a pathological entity is medically significant. It serves as a marker of deviation in normal homeostasis, especially in oxygen saturation to brain signalling and activities. When breaching normal threshold after a drug intake, simple yawning is termed as "Pathological Yawning" (PY) and is reported to be a side-effect of the drug.

**Figure-3.** Network showing the pathological yawning associated genes and their disease network



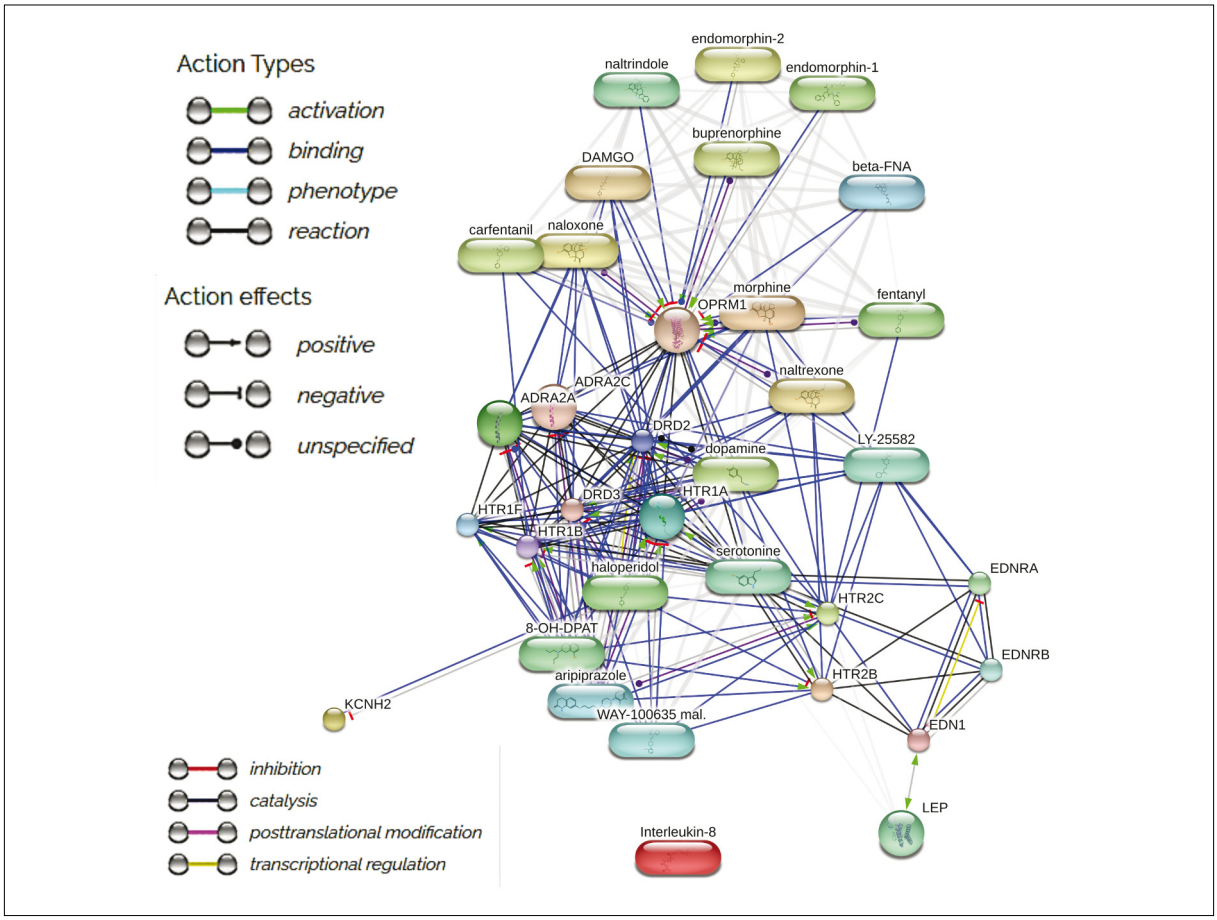

The Red-orange nodes are the gene and gene products while the blue ones are the disease-disorders that these genes are commonly associated with

Literature associates several psychiatric medications with PY (Lavertu et al., 2021). Though present study, resonates with this previous finding, it is also pertinent to note that antibiotics, vaccines, pain killers and even immunoglobulin injections have also been reported to trigger PY, albeit in small numbers. Yet this phenomenon warrants further investigations as some of it has been reported as life threatening or serious. The Figure-2 and Figure-3A as well as Table-2 indicate that certain inflammatory mediators work in tandem for PY. Hence, the role of inflammatory signals stimulating PY should be further explored.

About 48% of instances of PY in the USA database qualified to be a serious medical issue, with 15% of them requiring hospitalization and few deaths. Hence the occurrence of PY could indicate some severe complication brewing. The cause-effect cannot be explored using this database and long-term studies have to be performed to identify the relationship. At present in the clinics, PY cannot be ignored as it may be one of the earliest manifestations of vasovagal involvement (Shoja et al., 2009; Chronin, 1988). If left unattended, patient can potentially progress to a spectrum of medical condition- ranging from simple syncope to severe medical crisis (Millichap, 2014) Also, there may be sympathetic suppression related to yawning and altered ventilation during the phenomenon or an autonomic prodromal alteration (Mosqueda-Garcia et al., 2000; Wieling et al., 2009). The central nervous system having heightened sensitivity to electrophysiologic changes, which could cause neurologic symptoms much earlier than cardiovascular system (Donald & Derbyshire, 2004).

In vasovagal literature, yawning is considered as

**Figure-4.** The drug-gene interaction at the hippocampus level showing several types of interactions along with action effects




a marker of sympathetic and cardiovascular system alteration. It is an early sign of positive hemodynamic response in an impending syncope and in certain cases considered as body's mechanism against the syncope in pre-syncopal stage (Duque et al., 2019). Yawning was much pronounced in neurally mediated syncope as compared to others (Lipsitz et al., 1997). Though the role of such syncope is researched in psychiatric literature, the incidence of yawning has not been duly considered (Eccles et al., 2015; Leftheriotis et al., 2008).

The gene expression at hippocampus – hypothalamus (paraventricular nucleus) and its correlation with PY is interesting, as most of the serotonergic/dopaminergic drugs are associated with the PY, mental illness and psychiatric drugs that act at these areas. Hence, their actions and adverse reactions could be associated from here. The effects of such drugs in causing PY could be influenced by the dose, speed of administration, presence of disease, concomitant medications, cytochrome P family status (for drug metabolism) patient age and sex play a role in the predisposition to PY (Donald & Derbyshire, 2004).

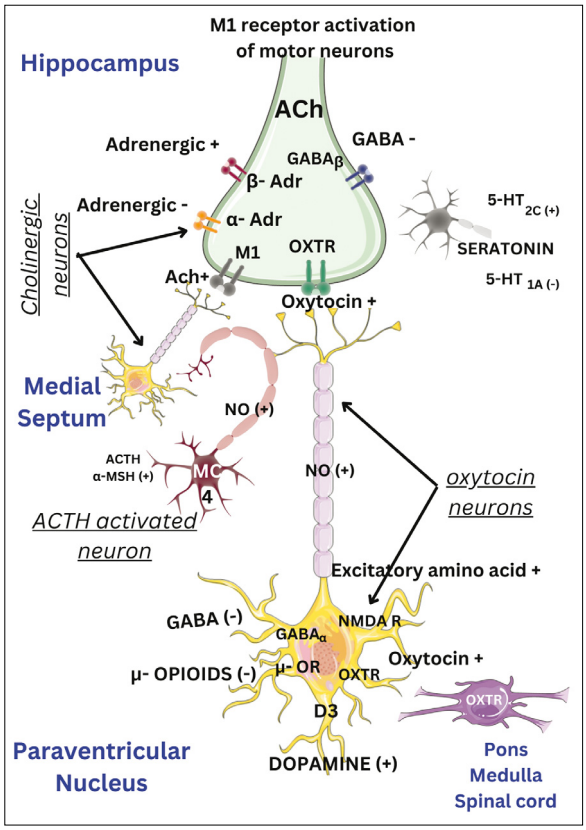
The current work attempted to identify some characteristics of the PY from adverse effect databases. The striking observation is the reporting of PY in post-vaccination for COVID19 in a significant population from Australian database while the same in USA database is very minimal. The occurrence of PY in post-vaccination for viral infection requires further validation. The PY is being increasing reported in adverse effect databases, possibly due to increasing awareness about medications and their side-effects. From the databases, the mean age of PY could be placed in the 5th decade of life with a slight female predilection, much similar to past studies (Sommet et al., 2007). With the psychiatric medications causing most PY, the psychiatrist needs to be aware of the condition to titrate their drugs.

More than 500 drugs are known to precipitate PY of which psychiatric drugs are the most common ones. There are many case reports and series in

psychiatric literature that discusses the PY (Béné et al., 2014; Bertschy et al., 1991; Blin et al., 1990; Patatanian & Williams, 2011; Roncero et al., 2013; Rothenberg, 2021; Uher et al., 2009). Lavertu A et al., derived a drug-risk profile (DRIP) score based on the severity of the adverse effect it produced. In this, higher score indicates higher risk. The scores for fluoxetine hydrochloride (2.48±0.21) followed by sertraline hydrochloride (1.77±0.08) and apomorphine hydrochloride (0.43±0.01) (Lavertu et al., 2021). On taking the Figure-3, Figure-4, Figure-5 together, it can be hypothesized that the certain genes associated with psychiatric disorders, drugs for mental illness and neurotransmitters associated with PY are overlapping. PY could be an inadvertent effect of the drug interacting with neurons. The PY could be thus, a marker for the need of titrating of these drugs in clinical practice.

From Figure-3, a section of common gene pathway associated with psychiatric disorders is identified. This concurs with Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium findings. ("Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium. Psychiatric Genome-Wide Association Study Analyses Implicate Neuronal, Immune and Histone Pathways," 2015). The gene products of ADRA2A and ADRA2C are alpha-2-adrenergic receptors, which play a role in the regulation of neurotransmitter release from sympathetic nerves and adrenergic neurons in the brain. The DRD2 and DRD3 gene products are dopamine receptors, which are involved in a variety of brain activities including movement, mood, cognition, and reward behaviour processing. The EDN1 gene product is endothelin 1, a potent vasoconstrictor peptide produced by vascular endothelial cells. The HTR1A, HTR1B, HTR1F, HTR2B, and HTR2C gene products are serotonin receptors that play key roles in various physiological processes including the regulation of mood, appetite, and sleep. The KCNH2 gene product is a potassium channel that plays key roles in a cell's ability to generate and transmit electrical signals. The LEP gene product is leptin, a hormone involved in the regulation of body weight. The OPRM gene product is the mu-opioid receptor, which mediates the effects of opioids such as morphine. As seen in Figure-5A, the gene products, collectively or as a single entity could be triggered to produce PY. Yawning is reported to be triggered by neurotransmitters such as dopamine and serotonin acting on their respective receptors in the brain. Additionally, factors such as tiredness

**Figure-5A.** The neuron and neurotransmitters involved in the triggering of the yawning at hippocampal region of brain



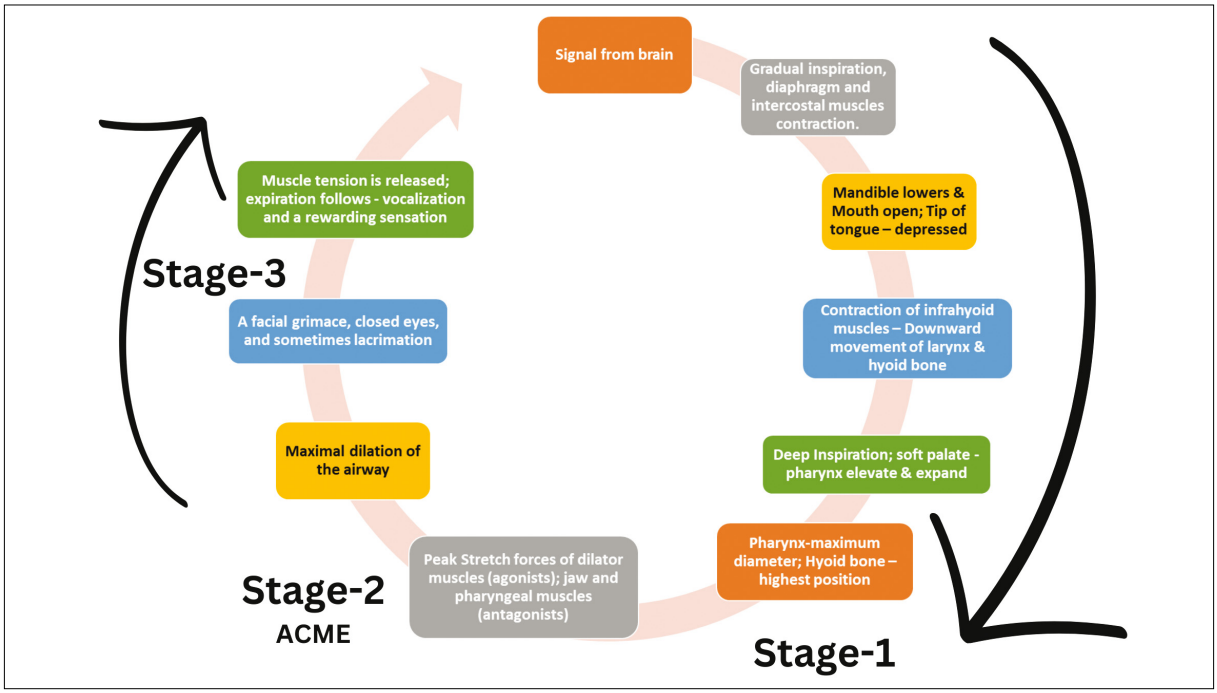

GABA – gamma-aminobutyric acid; OXTR – Oxytocin receptor; D–Dopamine; μ – Mu receptor; NMDA receptor – N-methyl-D-aspartate, also a receptor of glutamate; NO – Nitric Oxide; Ach – Acetylcholine; Adr – Adrenergic; HT – hydroxytryptamine receptors; ACTH – Adrenocorticotrophic; MC4 – Melanocortin 4; MSH – α-Melanocyte Stimulating Hormone; PVN – paraventricular nucleus

or hunger (which could be signalled by leptin levels) may influence yawning (Doelman & Rijken, 2022, Dourish CT & Cooper SJ, 1990, Krestel et al., 2018).

The complexity of the PY associated genes interaction as seen in Figure-4 at hippocampus and further strengthens this notion. Superimposing the PY mechanism (of Figure-3A) and the lessons from vasovagal literature, one could infer that PY would be a potential harbinger of neural alterations occurring at the brain stem level and immediate medical attention would be needed. In the neuro-psychiatry spectrum, PY, especially after psychiatric drug intake would warrant revisiting of the drug doses.

In addition, to the medical dimension, PY has socio-cultural connotations. Generally, psychiatric patients, in addition to the pre-existing stigma and social isolation could be plagued by PY. Yawning in several cultures have different connotation and

**Figure-5B.** The physiological steps involved in yawning




generally associated with sleep, boredom and laziness (Walusinski, 2010). PY could be conceived and misconstructed by care-givers and society in general. From the psychiatric patient perspective, PY due to medications turns into a constant companion, interrupting daily interactions and work schedule. Social situations may turn anxiety-inducing, as the yawning could draw unwanted attention and can be misinterpreted. Concentration and focus may suffer, making it difficult to engage in work or academic tasks, leading to a sense of frustration and diminished productivity. PY, if accompanied by fatigue and disrupted sleep pattern, it could impact overall well-being, leaving the patient feeling drained and mentally exhausted. Emotionally, the constant yawning could evoke feelings of self-consciousness and embarrassment, potentially compromising self-esteem in social situations and interaction. To patients, PY becomes a constant reminder of the medication's side effects and serves as a reminder of the ongoing struggle to find the right balance between symptom management and quality of life. Hence, a health care professional, particularly mental health professionals and neurologists should be aware of the importance of PY to deliver the best for the patients under their care.

The limitation of this study includes excessive relying on adverse event databases and curated databases. These inherently have bias including under-reporting or over-reporting of events, not being validated clinically by competent professionals and definitive clinical diagnosis. However, diagnosing yawning does not require much clinical skill, hence the chance of over diagnosis, should be conveniently ruled out. Future studies should be prospective in nature with adequately age, gender-matched controls. The pharmacovigilance department and experts should be roped in such studies to draw a meaningful conclusion.

## CONCLUSION

Yawning as physiological action, may lack the emotional appeal of clapping or crying, intensity of sneezing, the expressive quality of a genuine smile, nor provide soothing comfort of a warm touch or satiety after food. But never the less, it is a normal physiological action. But when occurring as a pathology triggered due to a medicine, the health care provider needs to explore the mechanism and silent signal that it sends. The results of this study indicates that the medical care professionals should be more diligent and educate their patients not to miss abnormally occurring normal physiological process such as yawning after drug intake. More active pharmacovigilance is needed to ensure absolute safety of the patients.

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# A pszichotróp gyógyszerek mellékhatásaként jelentkező kóros ásítás előfordulásának és etiopatogenezisének feltárása

**Bevezetés:** Az ásítás normális, sztereotip fiziológiai esemény az emberekben és az állatvilágban. Amennyiben túlzottan gyakori (>3/ 15 perc), akkor kóros ásításnak (PÁ) nevezzük. A PÁ-nak számos oka lehet, de leggyakrabban gyógyszerek mellékhatásával hozható összefüggésbe, különösen a pszichofarmakológiában használt gyógyszerek esetében. Bár vannak elszigetelt esetbeszámolók és esetsorozatok, a PÁ-val kapcsolatban nem állnak rendelkezésre jelentősebb vizsgálatok. Ez a munka ezt a hiányosságot igyekezett pótolni. **Módszere:** A jelen munka célja a PA jellemzőinek feltárása volt, Ausztrália (Database of Adverse Event Notifications), Kanada (Canada Vigilance Adverse Reaction Online Database) és az Amerikai Egyesült Államok (FDA Adverse Event Reporting System - FAERS) nem kívánatos mellékhatás-adatbázisainak adatai alapján. Ezek az adatbázisok összegyűjtik és nyilvános hozzáférést biztosítanak a gyógyszerekkel és terápiás termékekkel kapcsolatos nemkívánatos eseményekről szóló jelentésekhez. Elsődleges farmakovigilancia eszközként, valamint az egészségügyi szakemberek, kutatók, és a nyilvánosság számára első vonalbeli forrásként szolgálnak a gyógyszerek biztonságosságának nyomon követéséhez és megalapozott döntések meghozatalához. 2023 júniusának első hetében átvizsgáltuk a nyílt hozzáférésű, korlátozások nélküli gyógyszer mellékhatás adatbázisokat, az „ÁSÍTÁS" szót használva egyetlen keresőkifejezésként a gyógyszermellékhatások esetében, egyéb korlátozás nélkül. Összegyűjtötték a PA esetek adatait nemmel, életkorral, a gyógyszerhasználat okával, egyéb kísérő panaszokkal, valamint a mellékhatás(ok) jellegével és kezelési indikációjával együtt. Leíró statisztikai elemzéseket végeztünk. **Eredmény:** Az USA adatbázisában szereplő 2655 esetből 398 (15%) esetében több mint egy gyanús gyógyszer, összesen 578 gyógyszer volt érintett. A leggyakrabban érintett gyógyszerek az apomorfin, sertralin, fluoxetin és paroxetin voltak. Összesen 341 (12,8%) esetben szerepelt az ÁSÍTÁS önmagában vagy egy másik alvászavarral együtt, a leggyakoribb érintett szer a fluoxetin-hidroklorid volt. **Megbeszélés és következtetés:** A cikk kitér ásítás idegi mechanizmusára és fiziológiájára. Jelen tanulmány hangsúlyozza, hogy az egészségügyi szakembernek, különösen a mentális egészségügyi szakembereknek és a neurológusoknak tisztában kell lenniük a PÁ fontosságával, hogy a legjobb kezelést nyújthassák betegeik számára.

**Kulcsszavak:** kóros ásítás, mellékhatás, gyógyszerek, pszichiátriai gyógyszerek, neurológiai mellékhatások, etiopatogenezis