Progesterone Aids in Alleviation of Nicotine Withdrawal Symptoms: A Systematic Review

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Abstract

Background: A systematic review of studies on progesterone's usage in the cure of nicotine craving was undertaken. Progesterone is a steroid hormone that influences the reproductive system as well as γ-Aminobutyric acid type A (GABAA) receptors, glycine, kainite, and nicotinic receptors. It is thought that progesterone might help with nicotine withdrawal symptoms in addicted people.

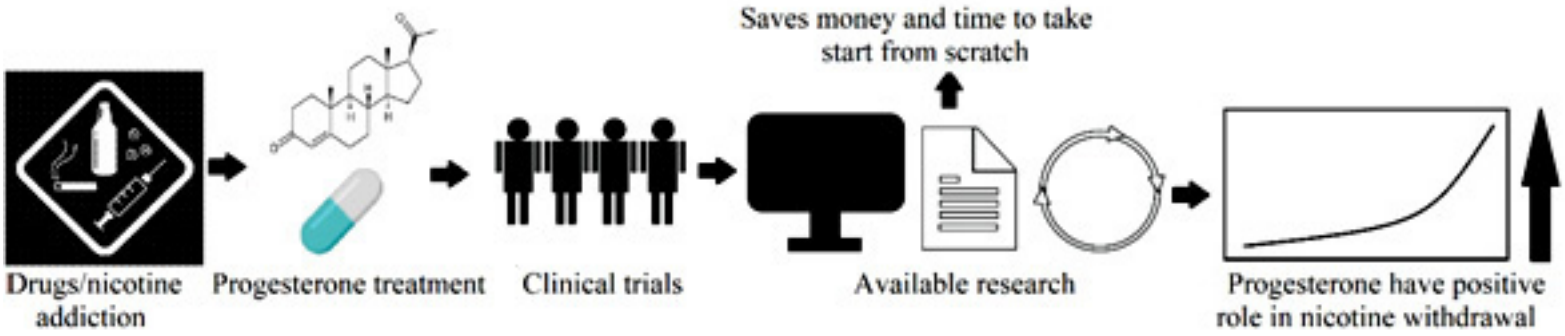
Method: Two authors completed the literature search independently using the Boolean search approach and searching key terms (i.e. progesterone AND treat*, drug addiction AND withdrawal, smok*, nicotine), screened the title, abstract and full-text for data extraction during June 2021. A search in the PubMed, NIH, Elsevier, Scopus, Web of Science, Google Scholar, and Science Direct databases was performed. The review included seven (7) articles out of seventy-eight (78) downloaded articles that met the inclusion criteria. Microsoft Excel and IBM SPSS were used for statistical analysis.

Results: These studies included 147 males and 377 females, out of which 46 were pregnant. The average age ranged between 18 and 45 years. The participants included those who had smoked 10-25 cigarettes/day for a year. The carbon monoxide measuring over 10ppm signifies recent smoking was found in 10% (n=12) participants who were given 400mg progesterone, 11% (n=14) for the 200 mg progesterone, and 13% (n=16) for the placebo groups. The progesterone prescription of 400 mg/day was effective in decreasing cravings to smoke, while the 200 mg dose helped with improving cognitive performance. Females in the progesterone group exhibited significantly lower smoking craving scores than females in the placebo group. A significant difference has been observed in 7-day PPA at week 4 among women i.e. "PRO: 18 (35.3%) vs. PBO: 9 (17.3%), Odds Ratio: 2.61 (95% confidence interval) and p=0.041", but not among men i.e. "PRO: 13 (23.2%) vs. PBO: 12 (21.1%), 1.13 (0.47, 2.76) and p=0.782". There was some evidence that PRO delayed relapse in women (Days to Relapse; PRO: 20.5 ±29.6 vs. PBO: 14.3 ±26.8, p=0.03) but not in men (PRO: 13.4 ±25.9 vs. PBO: 13.3 ± 23.8, p=0.69). Nearly half of the females who smoke before pregnancy can quit smoking during pregnancy. However, 40-52% reverts within 2 weeks while 70-80% resumes smoking within a year of childbirth.

Conclusion: In the majority of instances, 200mg was administered, and favorable outcomes were obtained. Although there were no major side effects observed, a few moderate side effects such as breast tenderness were reported in a few individuals. As a result, progesterone therapy helps to alleviate nicotine withdrawal symptoms, lowers smoking intensity, and treats smoking addiction in both men and women.

Keywords: progesterone, prescription, treatment, drug addiction, withdrawal, smoking, nicotine

Graphical abstract (adapted from Rasheed et al., 2022):



Introduction

The drug addiction has become one of the most serious problems in the contemporary world. Addiction is a lot like other diseases which disrupt the normal and healthy function of an organ in the body but can be preventable and curable in many cases. If left untreated, they can last a lifetime and may lead to death (Alfaifi & El-Setouhy, 2022). Drug addiction remains a substantial problem in the world specially nicotine addiction which is responsible for more than 480,000 deaths per year in the United States. Nicotine is a chemical found in tobacco and cigarettes. Nicotine addiction continues to be the main cause of preventable death in developed countries (Lynch and Sofuoglu, 2010). All the societies are trying hard to resolve it but they have very little success as yet.

Although nicotine use has leveled off in recent years, Perkins (2001) suggest that cigarette smoking is on the rise in young women and teen girls. Women appear to respond less favorably to smoking cessation treatments (Scharf & Shiffman, 2004), despite maintaining their nicotine addiction with lower levels of nicotine intake than men (Zeman et al., 2002). The mechanisms of these gender differences in nicotine addiction are not clear and may include the influence of cyclic changes in levels of the gonadal hormone progesterone across the menstrual cycle and at different hormone transition phases (i.e., adolescence, pregnancy, menopause).

Progesterone is a steroid hormone synthesized in the ovaries, as well as in the adrenal glands. Cyclic changes in progesterone take place during the menstrual cycle, which is divided into four phases: menstruation, follicular, ovulatory, and luteal. During the follicular phase, women have low progesterone levels that are comparable to those in men, less than 1 ng/ml (Pearson et al., 2000). Women have higher progesterone levels than men during the luteal phase of the menstrual cycle (2–28 ng/ml), and especially high levels during pregnancy (9–200 ng/ml; Buffet et al., 1998). The high levels of progesterone and progesterone metabolites fall rapidly and dramatically within 2 weeks following childbirth (Cunningham et al., 2005).

Progesterone have well documented actions on brain functioning, including interactions with multiple neurotransmitter systems affecting the brain reward circuit (Jackson et al., 2006). Cumulative evidence from preclinical and clinical studies suggest that gonadal hormones, especially progesterone, may protect females during initiation and maintenance of tobacco addiction, and may have therapeutic use for tobacco addiction, especially in female smokers (Allen et al., 2008; Sofuoglu et al., 2009; Sofuoglu et al., 2010). In the brain, progesterone binds to intracellular progesterone receptors found in the hypothalamus and many other brain regions (Brinton et al., 2008).

Progesterone itself or through its active metabolites, allopregnanolone and preganolone, interact with many other receptors in the brain including the GABAA, glycine, kainate, sigma1, and nicotinic receptors (Chesnoy-Marchais, 2009; Romieu et al., 2003;). Allen et al. reported that among women trying to quit smoking, those who were assigned to quit during the follicular phase of their menstrual cycle relapsed faster to smoking than those who quit during the luteal phase (Allen et al., 2008). Since the luteal phase of the menstrual cycle is characterized by higher progesterone levels, these findings support the contribution of progesterone to smoking relapse and warrant further studies aiming to better characterize progesterone's role in smoking relapse.

Significance of the research

Although multiple studies have demonstrated the influence of sex and menstrual cycle phase on nicotine withdrawal severity, smoking behavior, and treatment outcomes (Steinberg and Cherek, 1989; Perkins et al., 2000; Snively et al., 2000; Carpenter et al., 2006), but there exists a research gap on association exogenous administration of progesterone with nicotine addiction both in males and females. To fulfill this research gap, a systematic review was conducted of studies on progesterone used to treat nicotine addiction. Progesterone has many unique features as a relapse prevention intervention in postpartum women; it is a natural hormone commonly used by obstetricians and nurse practitioners/midwives, and is safe and well tolerated in this population, including those who are breastfeeding (Goletiani et al., 2007). It is postulated that progesterone can aid in symptoms of nicotine withdrawal in addicted population.

Objective

To investigate whether progesterone aids in alleviation of nicotine withdrawal in addicted population.

Methodology

Ethical review statement
No data was collected from human subjects directly by the authors, however, the research was conducted in adherence to the Declaration of Helsinki.

Data collection
A search in the PubMed, NIH, Elsevier, Scopus, Web of Science, Google Scholar and Science direct database was performed. The search was performed during June 2021 with the relevant keywords i.e. progesterone, treatment, drug addiction, withdrawal, smoking, nicotine. Seventy-eight (78) research articles were downloaded but after checking the inclusion criteria, only seven (7) research articles on progesterone having an association with nicotine withdrawal were selected. Inclusion criteria were specified in advance (Figure 1).

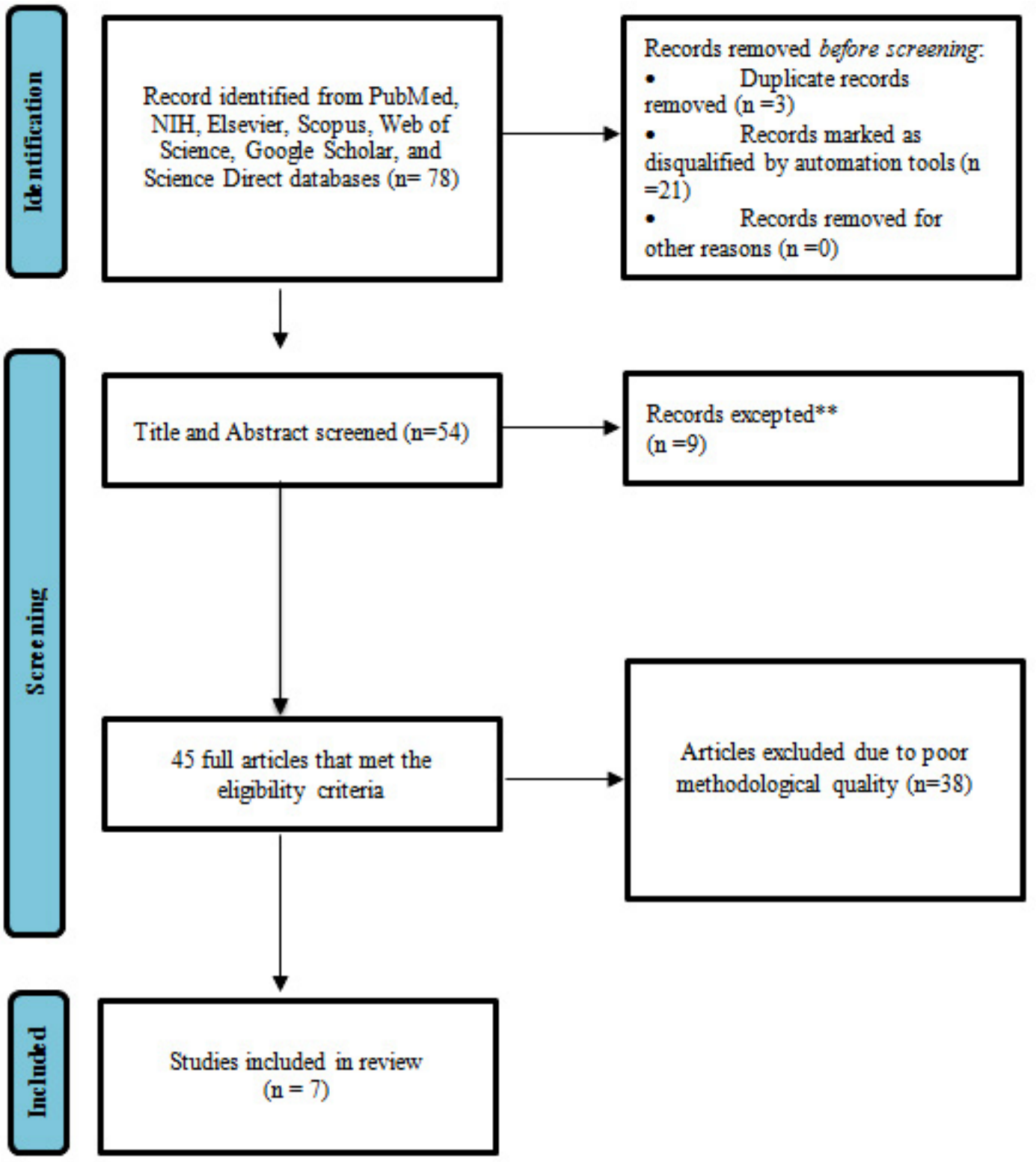
Inclusion Criteria
1. Progesterone and nicotine withdrawal studies of human.
2. Randomized controlled trials, and controlled trials or observational studies with comparators, were included.
3. Original research articles published in PubMed recognized journal.
4. Research articles published since 2009.

Exclusion Criteria
1. Progesterone and nicotine withdrawal studies on animals.
2. Research articles published before 2009.
3. Articles not written in English.

Limitation
Current research has the following limitations.
1. Studies conducted on human.
2. The search was restricted to publications since 2009.
3. Electronic medical databases for data collection.
4. Ethical approval was not required for this systematic review of published papers.

Statistical analysis
Statistical analysis was implemented through Microsoft Excel (version 2016) and IBM SPSS (version 25) for Windows.

Figure 1. PRISMA flowchart illustrating the study process for systematic review of progesterone effects on nicotine withdrawal. **Records excluded due to unavailability of sufficient data. 7 studies were selected for this review after screening for eligibility



Results

The study conducted by Sofuoglu et al. (2009) was double-blind, placebo-controlled, crossover study. Both physiological and subjective outcomes were measured. Physiological outcomes were systolic and diastolic blood pressure and heart rate while Drug Effects Questionnaire, Brief Questionnaire on Smoking Urges (BQSU), Nicotine Withdrawal Symptom Checklist (NWSC) and Profile of Mood States (POMS), measured the subjective outcomes. Progesterone did not affect the response of nicotine on the physiological measures as compared to placebo ($p>0.05$ for heart rate, systolic blood pressure and diastolic blood pressure). In case of subjective outcomes progesterone significantly enhanced the "bad effect" ($p<0.05$) and lowered "drug liking" ($p< 0.05$). BQSU showed a significantly higher total score and score for "urge to smoke for stimulation" in placebo group as compared to the treatment group. POMS and NWSC scales did not show significant differences between the two groups (Table 1).

In another study by Sofuoglu et al. (2011), the effects of 200mg progesterone, 400mg progesterone and placebo were compared. Heart rate and diastolic blood pressure were significantly lower in 200mg progesterone, 400mg progesterone groups as compared to placebo in males. Women showed a significantly lower blood pressure values for 400mg progesterone as compared to placebo. Alveolar carbon monoxide levels indicating recent smoking were significantly lower in 400mg progesterone group (10%) and 200mg progesterone group (11%) as compared to placebo (13%). However, the results were not significant. Saliva cotinine levels and number of cigarettes smoked were also not significant between the 200mg, 400mg and placebo groups. Cognitive performance, measured by Digit Symbol Substitution Test (DSST) showed significantly higher scores in 200mg group as compared to 400mg and placebo groups (Table 1).

In the study by Saladin et al. (2015), plasma ovarian hormone levels in freely cycling female smokers were correlated self-reported abstinence and carbon monoxide levels <10ppm. They showed that one standard deviation unit increase in progesterone increased the odds of abstinence by 20% and one SD increase in progesterone to estradiol was associated with 13% increased odds of abstinence (Table 1).

Allen et al. (2016) compared the abstinence at weeks 4 and 12 and relapse rate among the postpartum females who took 200 mg progesterone twice daily and those who took placebo. They found that at week 4, 75% of the women in the treatment group and 68.2% of the females in the placebo group remained abstinent. At 12 weeks, 54.2% of the females in the progesterone group and 40.9% of the women in the control group achieved abstinence (Table 1).

Forray et al. (2017) reported that the women who took progesterone 200mg twice daily were 1.8 times more likely to attain abstinence during eight weeks and took longer to revert back to smoking as compared to placebo group (10 vs 4 weeks). However, these results were not statistically significant. The craving rate reduced by 10% per week, in the progesterone group as compared to the placebo group (Table 1).

Tosun et al. (2020) studied the effect of 200mg twice-daily progesterone tablets on self-reported 7-day point prevalence abstinence, prolonged abstinence urine cotinine levels and breath carbon monoxide levels. They concluded that women in the treatment group had 2.6 times higher chance of achieving 7-day point prevalence abstinence at week 4 as compared to placebo group. All other outcomes were not significantly different between treatment and placebo groups in both males and females (Table 1).

Allen et al. (2020) compared the puff volume between the females taking progesterone and those taking placebo in a double blind, counterbalanced, cross over randomized trial. They concluded that the cumulative puff volume was significantly lower in the progesterone group (1186 ml vs 1486 ml) ($p= 0.01$). The average puff volume and number of puff was also lower in the progesterone group but the results were not statistically significant (Table 1).

Table 2 and Figure 2 summarizes the impact of progesterone from the selected studies and it has been found that five out of seven researches have tested 200mg of progesterone (figure 2a). Figure 2b shows that six in seven studies have reported positive effects of progesterone i.e. aids in alleviation of nicotine withdrawal symptoms. Furthermore, it was noted that only a single study has observed general adverse symptoms, two reported breast tenderness while four did not found any adverse effects.

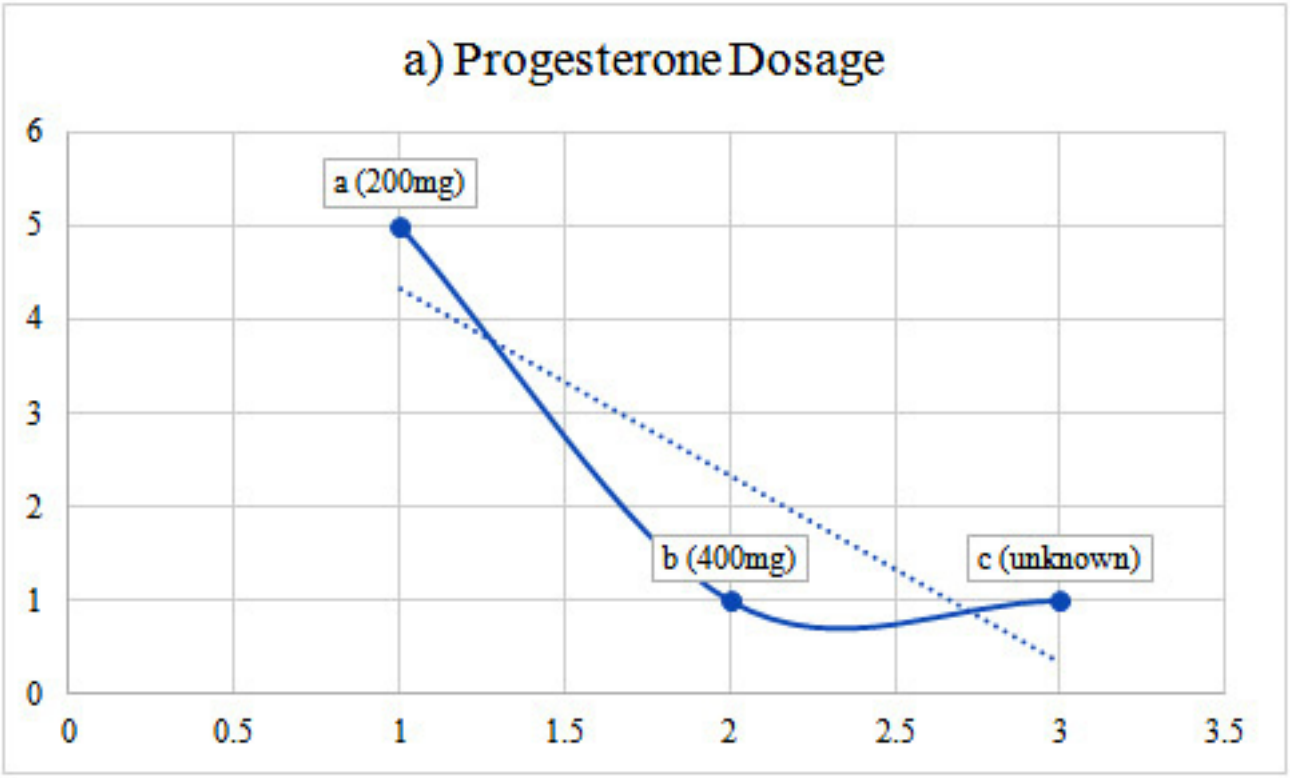
Table 1. Association between progesterone administration and nicotine withdrawal symptoms

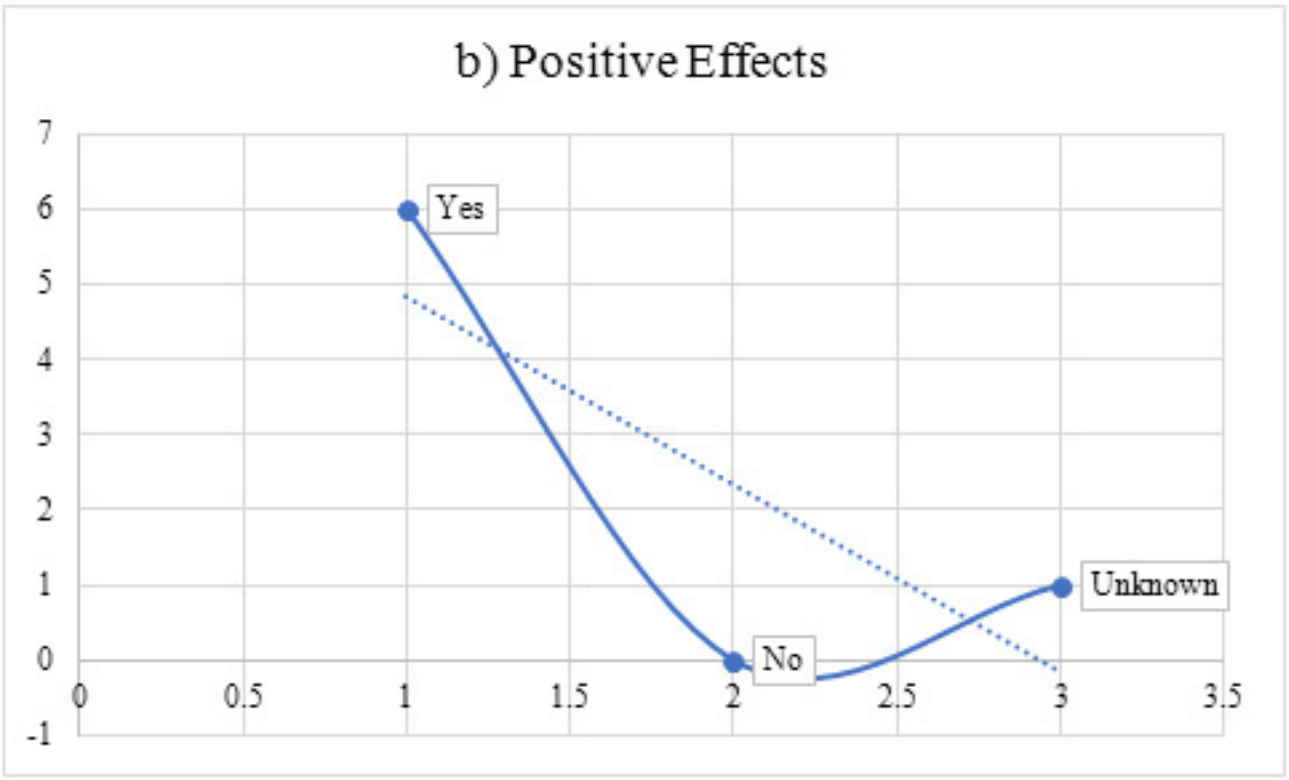
Authors	Population	Age	Gender	No. of cigarette smoked/day	Days cigarettes left	Progesterone dosage	Results	Adverse effects
Sofuoglu et al., 2009	12	30-40	6 males & 6 females	15-20	No smoking on experimental day	1 dose of 200 mg progesterone	Progesterone treatment enhanced nicotine's effect in suppressing urges for smoking,	Opposite effects on the aversive and pleasurable effects of nicotine, simultaneously enhancing ratings of ''bad effect'' while attenuating ''drug liking.''
Sofuoglu et al., 2011	64	30-35	34 males & 30 females	15-18	The first 3 days of treatment period, smokers abstained from smoking	200 or 400 mg/day progesterone or placebo given in two separate doses	Progesterone at 400 mg/day was associated with reduced urges for smoking but did not change ad lib smoking behavior. Progesterone treatment also attenuated urges for smoking and some of the subjective effects from smoking.	Unknown
Saladin et al., 2015	108	18–45	108 females	≥10/ 17±7.3	Smoked for at least the past 6 months	Varenicline tablets, placebo patches (tablets) and nicotine patches	Increasing levels of progesterone may have a dominant role in the hormonal milieu of free cycling women and that this dominance may yield benefits as they attempt to quit smoking	Unknown
Allen et al., 2016	46	18–35	46 females	10-15	Unknown	200mg twice a day	A higher prevalence of abstinence at week 4 in the PRO group was observed. Less depressive symptoms were reported	Fatigue, nausea, breast tenderness, spotting, weight gain; 10/46 participants reported daily vaginal bleeding
Forray et al., 2017	41	18–42	41 females	≤10	32 weeks	200 mg twice daily	There was a 10% greater decline per week in craving ratings in the progesterone group compared to placebo	No serious adverse events occurred
Tosun et al., 2019	216	18-60 (male), 18-50 (female)	113 males & 103 females	≥5	7 days	200 mg twice daily	200mg twice daily of oral micronized progesterone may be effective for smoking cessation in women, but not in men.	Unknown
Allen et al., 2020	43	18-40	43 females	≥5	Midnight of the experimental day	200 mg twice daily	Progesterone administration has the potential to reduce smoking intensity after overnight abstinence in women of reproductive age.	Breast tenderness

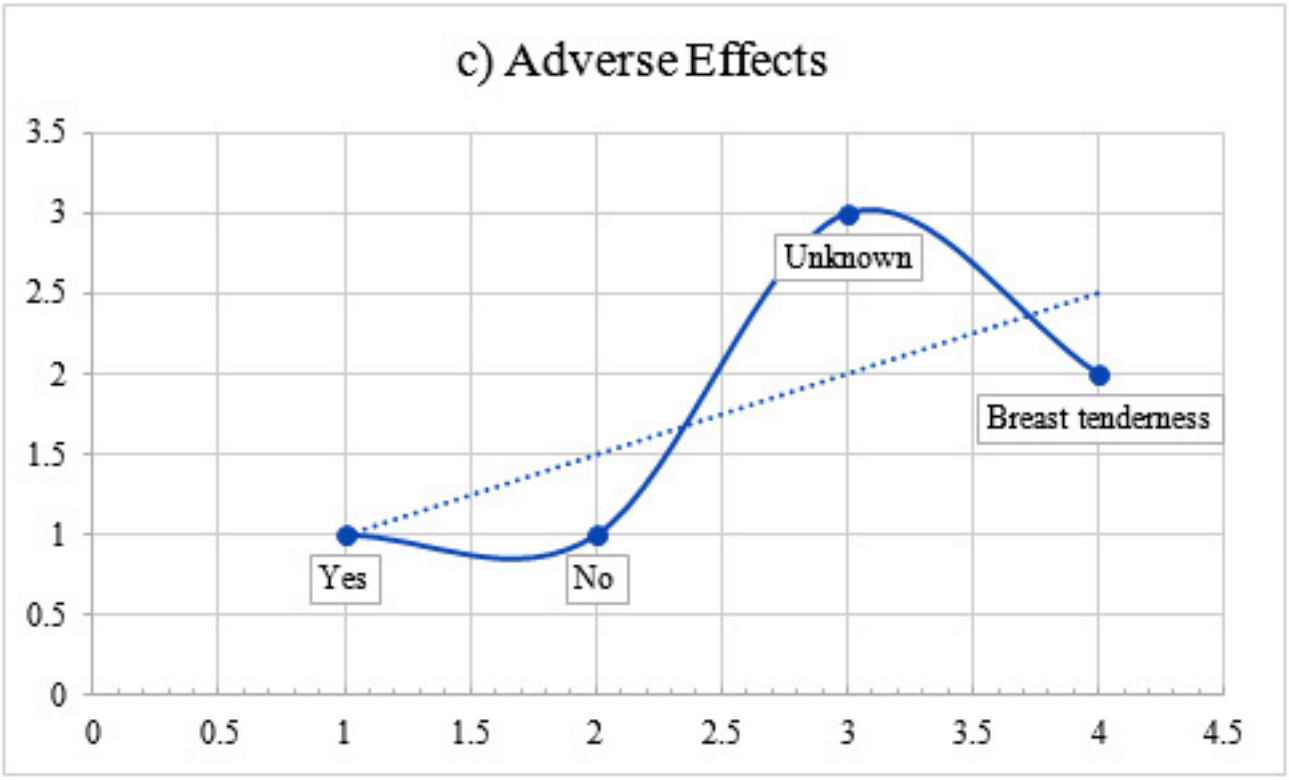
Table 2. Summary of the progesterone dosage and its effects

	Frequency	Percent	Valid Percent		Cumulative Percent
Progesterone dosage	200mg	5	71.4	71.4	71.4
	400mg	1	14.3	14.3	85.7
	Unknown	1	14.3	14.3	100.0
	Total	7	100.0	100.0	
Positive effects	Positive	6	85.7	85.7	85.7
	Unknown	1	14.3	14.3	100.0
	Total	7	100.0	100.0	
Adverse effects	Adverse effect	1	14.3	14.3	14.3
	Unknown	3	42.9	42.9	57.1
	Breast tenderness	2	28.6	28.6	85.7
	None	1	14.3	14.3	100.0
	Total	7	100.0	100.0	

Figure 2a) dosage of progesterone used in the selected studies; b) positive impacts of progesterone in alleviation of nicotine withdrawal symptoms; c) adverse effects of progesterone on patients.




b) Positive Effects
7
6
5
4
3
2
1
0
-1
0
0.5
1
1.5
2
2.5
3
3.5
Yes
No
Unknown


c) Adverse Effects
3.5
3
2.5
2
1.5
1
0.5
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
Yes
No
Unknown
Breast tenderness

Discussion

The pathophysiology of nicotine addiction

Several neurobiological models involving many neurotransmitters have been described to explain the pathophysiology of nicotine addiction and withdrawal. Most of these studies have been conducted in animal models. Nicotine has been shown to exert its effects by binding to nicotinic acetylcholine receptor (nAChR). This receptor consists of 16 subunits (Arneric et al., 1995; Wonnacott, 1997). The subunits that are present in the nervous system are α2-α8 and β2-β4 among which β2 contains highest affinity for nicotine (Picciotto et al., 1995).

Dopamine plays the central role in the positive reinforcement effects of nicotine. Dopamine is an integral part of reward circuit and the presence of nAChRs in the dopaminergic neurons causes nicotine addiction. Dopamine is released when nicotine binds to nAChRs in the mesolimbic system specifically in ventral tegmental area (Nisell et al., 1994). Several other neurotransmitters also regulate the release of dopamine by dopaminergic neurons in response to nicotine. This is due to the presence of nAChRs in several pathways, which converge on the dopaminergic neurons in the ventral tegmental area that in turn projects to the nucleus accumbens. These pathways include the following;

1. Nicotinic AChRs are present on the presynaptic glutamatergic afferents, which release glutamate. Glutamate in turn activate VTA neurons by NMDA receptors to release dopamine in nucleus accumbens (Shelly et al., 2000).
2. Many nAChR containing cholinergic efferents from pedunculopontine nucleus synapse upon the VTA neurons and cause dopamine release from VTA neurons.
3. The role of sertonergic system in mediating the positive reinforcement of nicotine has not been well described. Nicotinic ACh receptors are also present in the Raphe nucleus and hippocampus that directly project to nucleus accumbens. The neurons mediate their addictive effects by releasing serotonin.
4. The neurotransmitter gamma-aminobutyric acid (GABA) also controls the release of dopamine from ventral tegmentum (Kalivas et al., 1993). GABA releasing neurons inhibit the release of dopamine from VTA (Walaas & Fonnum, 1980; Yim & Mogenson, 1980). In addition, many inhibitory GABAergic interneurons are also present in the VTA and nucleus accumbens that inhibit dopamine release (Kalivas et al., 1993).
5. Nicotine also stimulates opioid release in nucleus accumbens (Houdi et al., 1991; Pierzchala et al., 1987). Nicotine causes the release of ligands that occupy the μ-opioid receptors (Davenport et al., 1990).

Role of Progesterone in the treatment of different diseases

Progesterone is produced in the ovaries and the adrenal glands. It undergoes cyclical changes in the menstrual cycle. Lower levels are present during the follicular phase and they increase during luteal phase of menstrual cycle and pregnancy (Buffet et al., 1998). Progesterone has been used in the treatment of several reproductive and non-reproductive diseases like ovarian failure, premenstrual symptoms, amenorrhea, dysfunctional uterine bleeding, menopausal symptoms, and for contraception (de Lignieres, 1999). Its use in traumatic brain injury and seizures is being investigated (Herzog, 2008; Stein, 2008). Progesterone as an oral drug has a lower bioavailability because it undergoes first pass metabolism and is absorbed poorly (Lynch, 2013). Many synthetic progesterone derivatives have been developed to overcome this but they have side-effects like fluid retention, androgenic effects and dyslipidemia (Goodman et al., 1996). Micronized progesterone has been developed to overcome these side effects and increase the bioavailability.

Role of Progesterone in Nicotine Withdrawal

Progesterone is not only a reproductive hormone but it is also involved in neural signaling. Progesterone and its metabolites act upon many neurotransmitter receptors which have been described above. Many of these are involved in neurobiology of nicotine addiction like GABA, glycine, sigma1, kainate, serotonin3, and nicotinic cholinergic receptors (Cyr et al., 2000; Romieu et al., 2003; Smith et al., 2007). The main effect of progesterone on nicotine reward circuit is through GABA (Lynch, 2013). GABA as described above is an inhibitory neurotransmitter in many areas of central nervous system including the dopaminergic pathways involved in reward circuit. Progesterone stimulates GABA release that in turn inhibits the nicotine reward circuitry (Lynch, 2013). In a study by Allen et al. (2008), it was observed that the women who gave up on smoking during the follicular phase of the menstrual cycle were more prone to relapse than those who quit smoking during the luteal phase. These findings, in addition to the fact that changes in reward circuit have been observed during different phases of the menstrual cycle, led to the hypothesis that progesterone may help in nicotine withdrawal since its levels are higher during the luteal phase (Dreher et al., 2007).

Although progesterone has been shown to be protective against nicotine withdrawal, it also reduces smoking intensity (Schiller et al., 2012). In addition, progesterone is also helpful in preventing smoking initiation and as a treatment of smoking addiction. In general, progesterone also reduces drug-taking behavior. This may be due to the effect of progesterone on reward pathway. Many preclinical studies have demonstrated this effect (Lynch et al., 2010). However, Sofuoglu et al., 2011 showed that 400mg progesterone decreased the urge to smoke in abstinent smokers but did not change the ad lib smoking behavior. This may be due to underlying psychological factors that may be reinforcing the smoking behavior. Another bias may be due to the enrolment of the participants who were not already seeking treatment for smoking cessation (Sofuoglu et al., 2011).

Tosun et al. removed this bias by including those patients who were willing to quit smoking and scores ≥7 on Likert scale. They also included males in their study. The results

showed that progesterone was superior in achieving 7-day point prevalence abstinence at week 4 in females only. Seven-day point prevalence abstinence at weeks 8 and 12 was not significantly higher in the progesterone group in both males and females. This study only included premenopausal females who have variations in the endogenous levels of progesterone (Tosun et al., 2019). In the study by Saladin et al, premenopausal women who were attempting to quit smoking by using either transdermal nicotine patches or verenicline were recruited. The levels of endogenous ovarian hormone were associated with 7-day point prevalence abstinence in varenicline treated and transdermal nicotine patches treated female smokers. The effects of varencline and nicotine patches may mask the effect of progesterone in nicotine withdrawal (Saladin et al., 2015).

Allen et al., 2016 found a higher abstinence rates at week 4 and 12, however, the results were not statistically significant. They included the women in their postpartum period who might have avoided smoking due to breast feeding. This may have resulted in higher abstinence rates in the placebo group as compared to the other studies. The results ae also less generalizable as they have been validated on a specific sub-group of patients (Allen et al., 2016).

Conclusion

In the majority of instances, 200mg was administered, and favorable outcomes were obtained. Although there were no major side effects observed, a few moderate side effects such as breast tenderness were reported in a few individuals. Hence, the review suggests that progesterone therapy helps to alleviate nicotine withdrawal symptoms, lowers smoking intensity, and treats smoking addiction in both men and women.

Areas of Further Research

Although smoking is much prevalent in men also, only two studies included males in the randomized control trials. Majority of progesterone involved only the female participants. Most of the studies showed that progesterone is superior to placebo in achieving abstinence and lesser relapse rates but the results are not statistically significant in most cases. This may be due to small sample sizes in most studies. Inclusion of males in larger trials after establishing the safety of progesterone in male participants is required to study the universal effects of progesterone in smoking withdrawal. Another thing to be noted is that the abstinence rate also decreases in long term. Maximum rate is observed in week 4 with the rate decreasing over time up to week 12. Oral contraceptive pills containing progesterone should also be evaluated for the treatment of smoking withdrawal and prolog abstinence rates. Smoking is also related to psychological stress and depression. Almost all of the studies used different tools to assess self-reported abstinence, cognitive functions, and withdrawal symptoms. The role of depression and stress as a cause of lower abstinence rates and relapse of smoking over long term should be evaluated as a confounding factor.

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