Drugs of Abuse and Immuno-Modulation

NASHWA MAHMOUD RADWAN, M.D.

National Egyptian Center of Clinical and Environmental, Toxicological Research (NECTR), Faculty of Medicine, Cairo University.

Abstract

Introduction: Drugs of abuse are in fact associated with increased susceptibility to infectious diseases, especially opportunistic intracelular microbial infection and HIV infection. The effects of morphine on immune system are mediated through central as well as peripheral mechanisms.

The immune system of drug dependent individuals is known to be suppressed, dysfunctional and hyper stimulated.

Objective: To determine the level of proinflammatory cytokines in opiate, cannabinoid and tramadol addicts.

Subjects and Methods: The studied population comprised 80 individuals divided into 4 groups:
1- 20 individuals are opiate addicts.
2- 20 individuals are cannabinoid addicts.
3- 20 individuals are tramadol addicts.
4- 20 individuals as control group.

They are all males and matched with the control group as regards socioeconomic status and smoking habits. All subjects were interviewed with a detailed questionnaire about presence of respiratory and skin symptoms. Detailed personal, medical examination was done. Determination of the level of interleukin 1, tumor necrosis factor alfa and inter leukin 6 (IL1, TNFα, IL6) in the serum was performed. Toxicologic screen was done and total leucocytic count was done as well.

Results: Respiratory and skin manifestations showed a statistically significant difference between addicts and control group.

Level of cytokines (IL6, TNFα, IL1) showed a statistically significant difference between addicts and control group. In correlation with the duration of addiction and age, a statistically significant negative correlation was found between opiate and cannabinoid addicts and control group as regards the level of cytokines. Total leucocytic count of the studied groups showed that addicts had higher values.

Conclusion: The results strengthen the relationship between addictive drugs especially opiates and cannabinoids and immune-modulation documented by low levels of proinflammatory cytokines (IL6, TNFα, IL1). Tramadol addiction had unique effect on cytokines level.

Key Words: Drugs of abuse – Proinflammatory cytokines.

Introduction

THE use of recreational drugs of abuse has generated several and serious health problems. There is a long-recognized relationship between addictive drugs and increased levels of infections. The effects of opiates or cannabinoids on the immune system are receptor mediated, occurring both directly via specific receptors on immune cells and indirectly through similar receptors on cells of the nervous system. There have been numerous clinical reports on the association between infectious diseases and use of illegal drugs. Experimental studies using drugs of abuse support the clinical observations that these substances are associated with immunomodulation [1].

Both exogenous and endogenous opioids exert some effect upon the immune system. They are seen to cause immunosuppression in man.

Opiates especially morphine lead to delayed neutrophil recruitment and increased bacterial burden in the lung, spleen and blood [2]. Cannabinoids especially the major psychoactive components tetrahydrocannabinol (THC), exert immunomodulatory effects that alter normal functions of T and B lymphocytes, natural killer (NK) cells and macrophages in human and animals [1].

Tramadol is a centrally acting analgesic, but is atypical in having at least two complementary mechanisms of action. It is an agonist at mu delta and kappa-opioid receptors with greater affinity for the mu-receptor. Other mechanisms that contribute to its analgesic affect are inhibition of neuronal re-uptake of norepinephrine and serotonin. As a result, tramadol-induced analgesia is only
partially antagonized by the opioid antagonist naloxone. It is also antagonized by α2 adrenoceptor antagonists [3].

Clinical, hematological and histopathological investigations revealed no drug-related changes following repeated oral and parenteral administration for 6-26 weeks to rats and dogs, as well as oral administration for 12 months to dogs. Only with doses for above those used in therapy, changes in general behavior, immunological and C.N.S. effects [4].

Aim of the study:
1- To assess the immune response in opiates and cannabinoid addicts.
2- To evaluate the impact of addiction on the susceptibility of the addict to infection.
3- To investigate the role of proinflammatory cytokines in addicts on to opiate, cannabinoid, tramadol.

Subjects and Methods

This study was done to examine sixty addicts and they were matched with twenty controls as regards age, smoking habits and socioeconomic status. At NECTR, from Jan. 2009 to Jan. 2010.

The duration of abuse is at most importance in judge correlation between addiction & immune modulate. So, all groups had been chosen from chronic abusers i.e. the duration is more than 5 years.

Both groups were interviewed using a questionnaire including personal history, smoking habits and current respiratory symptoms. Thorough clinical examination was performed with special emphasis to the respiratory system and skin. A written consent was obtained from each subject after explaining to him the aim and importance of the work. Investigations including toxicologic screen and determination of tumor necrosis factor alfa (TNFα), interleukin 1 (IL1) and interleukin 6 (IL6) were performed.

For all measurements, 5ml of venous blood was taken into a vacutainer tube and immediately centrifuged at 5000 rpm/min. serum was stored at-80°C until analysis. Serum levels of IL-6, IL-1 beta and TNFα were measured by ELISA kit supplied by (Quantakine R & D system USA) according to manufacturers instruction [5,6,7].

Toxicologic screen using Viva apparatus for determination of the type of the drug or substance abused. Chemical analysis was performed for total leucocytic count.

For statistical assessment

Data handling and Statistical Analysis:

Data were collected, checked, revised and entered the computer. Data were analyzed by SPSS statistical package version 17. Excel computer program was used to tabulate the results, and represent it graphically.

Qualitative variables were expressed as count and percentages.

The significant difference in distribution were tested by using Chi-square-test at p<0.05.

The significant difference between groups were tested by using One Way ANOVA.

Pearson correlation coefficient was calculated to show the power and direction of the linear relationship between the measured quantitative variables at p<0.05 [8].

Results

Table (1): Shows the demographic characteristic of addicts and control, both groups are matched as regards the age. The smoking habit is shown in the same table: in which 50% of tramadol addicts are smokers, whereas 90% of opiate addicts are smokers, and 90% of opiate addicts are smokers, however, 80% of cannabinoid addicts are smokers, and only 40% of control group are smokers.

Table (2): Shows the comparison between addicts and control group as regards the manifestations in the form of cough, sputum and or boils, abscesses. There are a statistically significant difference between addicts and control regarding both respiratory and skin manifestations.

Table (3): Shows a statistically significantly inhibition of the level of cytokines (IL6, IL1, TNFα) between opiate and cannabinoid addicts compared to the control group.

It showed also a statistically significant elevation of the level of cytokines: (IL6, IL1, TNF α) between tramadol addicts and control group.

Table (4): Shows a negative correlation between the level of cytokines and the age and the duration of opiate addiction i.e. the higher the duration of opiate addiction, the lower the level of cytokines.

Table (5): Shows a negative correlation between the level of cytokines and the duration of addiction
and age of cannabinoid addicts i.e. the degree of inhibition of cytokines is increased with the duration of addiction of cannabinoids and the age of the addict.

Table (6): Shows a statistically significant difference between addicts and control group as regards the total leucocytic count (TLC).

Table (1): Demographic characteristics among control and the addict groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean/year S.D</th>
<th>Mean/year S.D</th>
<th>Mean/year S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>27.5</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Tramadol addicts</td>
<td>28.00</td>
<td>2.51</td>
<td></td>
</tr>
<tr>
<td>Opiate addicts</td>
<td>31.30</td>
<td>3.11</td>
<td></td>
</tr>
<tr>
<td>Cannabinoid addicts</td>
<td>26.50</td>
<td>2.06</td>
<td></td>
</tr>
<tr>
<td>Smoking habit:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>8</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Tramadol addicts</td>
<td>10</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Opiate addicts</td>
<td>18</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Cannabinoid addicts</td>
<td>16</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

No significant difference in ages between groups by using independent t-test at \( p<0.05 \).
All studied group are males.
No significant difference in smoking habits between groups by using chi-square test of distribution at \( p<0.005 \).

Table (2): Comparison between addicts and control group Regarding clinical manifestations.

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Respiratory</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Tramadol addicts</td>
<td>10*</td>
<td>15*</td>
</tr>
<tr>
<td>Opiate addicts</td>
<td>18*</td>
<td>75.0</td>
</tr>
<tr>
<td>Cannabinoid addicts</td>
<td>16*</td>
<td>60.0</td>
</tr>
</tbody>
</table>

\( p \)-value: Significant difference

\(*=\) significant difference about control by using Chi square test at \( p \)-value \( <0.05 \).

Table (3): Comparison between addicts and control group as regards the Level of cytokines (IL6, IL1, TNF \( \alpha \)).

<table>
<thead>
<tr>
<th>Group</th>
<th>IL6 Mean±S.D</th>
<th>IL1 Mean±S.D</th>
<th>TNF ( \alpha ) Mean±S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>266.42±41.13</td>
<td>1.33±0.49</td>
<td>15.12±4.86</td>
</tr>
<tr>
<td>Tramadol addicts</td>
<td>770.47±252.80</td>
<td>7.99±2.09</td>
<td>29.79±9.05</td>
</tr>
<tr>
<td>Opiate addicts</td>
<td>150.97±40.22</td>
<td>0.82±0.33</td>
<td>8.33±0.68</td>
</tr>
<tr>
<td>Cannabinoid addicts</td>
<td>179.10±27.99</td>
<td>1.28±0.37</td>
<td>8.80±0.54</td>
</tr>
</tbody>
</table>

\( p \)-value: Significant difference

\(*=\) significant difference about control by using One Way ANOVA at \( p<0.05 \).

S.D = Standard Deviation.
There is a significant difference between addict groups and control group by using One Way ANOVA at \( p<0.05 \).

Table (4): Correlation between different parameters of cytokines with age and duration of addiction among opiate abusers (n=20).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age (years)</th>
<th>Duration of addiction (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Duration of addiction (years)</td>
<td>0.93**</td>
<td>—</td>
</tr>
<tr>
<td>IL6</td>
<td>-0.92**</td>
<td>-0.86**</td>
</tr>
<tr>
<td>IL1</td>
<td>-0.15</td>
<td>-0.16</td>
</tr>
<tr>
<td>TNF ( \alpha )</td>
<td>-0.31</td>
<td>-0.52*</td>
</tr>
</tbody>
</table>

\( ** =\) Pearson Correlation is significant at the 0.001 level of significant.
\( * =\) Pearson Correlation is significant at the 0.05 level of significant.

Table (5): Correlation between different parameters of cytokines with age and duration of addiction among cannabinoid abusers (n=20).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age (years)</th>
<th>Duration of addiction (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Duration of addiction (years)</td>
<td>0.96**</td>
<td>—</td>
</tr>
<tr>
<td>IL6</td>
<td>-0.90**</td>
<td>-0.84**</td>
</tr>
<tr>
<td>IL1</td>
<td>-0.39</td>
<td>-0.36</td>
</tr>
<tr>
<td>TNF ( \alpha )</td>
<td>-0.22</td>
<td>-0.12</td>
</tr>
</tbody>
</table>

\( ** =\) Pearson Correlation is significant at the 0.001 level of significant.
\( * =\) Pearson Correlation is significant at the 0.05 level of significant.
Table (6): Comparison between addicts and control group as regards the total leucocytic Count TLC.

<table>
<thead>
<tr>
<th>Blood picture</th>
<th>Tramadol (n=20) Mean±S.E</th>
<th>Opiate (n=20) Mean±S.E</th>
<th>Cannabinoid (n=20) Mean±S.E</th>
<th>Control (n=20) Mean±S.E</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>7.73±0.31</td>
<td>7.79±0.29</td>
<td>7.88±0.26</td>
<td>7.54±0.44</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

All values are expressed as Mean ± Standard Error. The significant difference between addict groups and control group by using One Way ANOVA at \( p < 0.05 \).

**Discussion**

Drug abuse is one of the serious problems that concern both the general population and the government. It affects young people in their reproductive years leading to many problems such as social maladaptation, decreased work productivity and job loss [5].

In the workplace, drug abuse is associated with absenteeism, infectious diseases, sleeping on job, interpersonal problems and poor job performance.

The relationship between the use of addictive drugs of abuse and the increased incidence of susceptibility to infectious diseases has been studied in recent studies. These studies have shown that drugs of abuse, including cannabinoids, opiates, and nicotine, alter not only neuropsychological and pathophysiological responses of individuals but also immune functions [9,10]. Experimental studies using drugs of abuse support the clinical observations that these substances are associated with immunomodulation [11,12].

Studies concerning the effects of addictive drugs on immunity become even more role of cytokines in immune response urgent with the onset of AIDS which is caused by human immunodeficiency virus (HIV) and results in a collapse of the immune system, making an individual highly susceptible to opportunistic microorganisms [13]. Drugs of abuse have been suggested as possible cofactors, resulting in a more rapid progression of the disease [14]. Opiates may promote immunodeficiency virus infection by decreasing the secretion of \( \alpha \) and \( \beta \) chemokines and at the same time increasing the expression of chemo-receptors CCR5 and CCR3 co receptors for the virus [15].

AIDS patients often use drugs such as cannabinoid, opiates and nicotine which some investigators think are immunosuppressive [16]. Opiates compose a collection of drugs derived from the poppy papaver somniferum which include opium, morphine and heroin [17]. Multiple immunomodulatory effects of opiates are transduced to immune effector cells mainly via the central nervous system e.g. by activation of the hypothalamus-pituitary adrenal axis [18,19] or directly via atypical opiate receptors or classic opiate receptor subtypes \( \mu \), \( \delta \), and \( \kappa \) present on immune cells.

Opiates are known to alter the release of hypothalamic-pituitary-adrenal HPA hormones (corticotrophin-releasing hormone and adrenocorticotropic hormone) [20], which in turn, alter glucocorticoids (cortisol and corticosterone), the end effectors of the HPA axis. The glucocorticoids play an important role in decreasing and regulating cellular immune responses [21].

In addition to these corticoids, immunosuppression via autonomic nervous system has been observed [22].

Studies have shown that morphine treatments suppress immune parameters in mice through the HPA axis [23]. Studies of drug addicts demonstrated a connection between drug use and infectious diseases [24,25].

Pulmonary infections caused by mycobacterial, staphylococcus, streptococcus, haemophilus and other bacteria, are among the most common diagnoses of opiate abusers [26]. The immunosuppression mediated by opiates may explain the increased incidence of infection among addicts [18].

These data are consistent with the results of the present study in which respiratory manifestations and infections are significantly higher among opiate addicts compared to the control group (Table 2).

Other serious diseases caused by microbial pathogens are endocarditis, abscesses and cellulitis, skeletal infections and hepatitis A, B and C [17,27].

Chronic morphine users and opioid abusers have inadequate wound closure and increased susceptibility to infection with altered expression of keratinocyte-derived cytokine and monocyte chemotactic protein [28].

These data are in accordance with our results in which there are higher prevalence of skin infections among opiate addicts (Table 2).
Therefore a correlation between the use of opiates and increased susceptibility to infection and depressed immunity does indeed exist. Whether this correlation due to increased exposure to infectious pathogens through risky behaviors, to immune suppressive effects of opiates, or to combination of these two is uncertain [25].

In vitro studies of immune cells have demonstrated receptors-mediated reduced phagocytes, chemotaxis, chemokine and cytokine production [8] which emphasize our results in which we found that the level of interleukin 1 IL1 and IL6 are less in opiate addicts compared to the control group (Table 3).

Chao, et al. [30] demonstrated that morphine inhibits the release of tumor necrosis factor in human peripheral blood which explain our results in which there are low levels of TNF in opiates addicts compared to the control group (Table 3). Shavity, et al. [31] observed that natural killer (NK) activity in rats was suppressed following morphine injection into the lateral ventricle of the brain via opioid receptors. The central opioid pathways were involved in immunosuppression of lymphocyte proliferation [32].

Morphine has been reported to alter immune function through induction of macrophage apoptosis [7].

The macrophages play a central role in innate and adaptive immunity [33]. They are fundamental cells of the innate immune response, and their ability to be chemotactically attracted to the site of initial microbial invasion or to an inflammatory focus is crucial for the full activation of the immune inflammatory response that follows. Macrophages are the main source of proinflammatory cytokines IL1 and TNFα as well as of the major anti-inflammatory cytokine IL 10 [34]. Macrophages also synthesize and release IL12, the critical factor deriving the development of Th1 cells. Morphine significantly modulates all macrophages functions. In fact, the administration of the drug led to decreased production of the proinflammatory cytokines IL1 and TNFα, in accordance with what we observed in the present study Table (3). Chronic morphine use impairs host innate immune response and increases susceptibility to bacteria and virus. [1] documented that in morphine-treated animals, a significant decrease in TNF-α IL1 and IL6 was observed before neutrophil recruitment.

Morphine uses multiple intracellular pathway to exert its generalized immunosuppression [35].

Opiates are typically associated with phenomena such as analgesia, respiratory depression, euphoria and addiction, which are mediated by three different opioid receptors [36]. In connection with the immune system, endogenous opioids, such as B-endorphin and exogenous opioids, such as morphine, are potent immunomodulators with inhibitory and stimulatory effects on immune function. These include lymphoid organ atrophy, changes in CD4 and CD8 expression in thymocytes, reduced natural killer cell activity [37], the balance between T helper type 1 and type 2 cells, liposaccharide-induced production of IL6 and TNF, activation of transcription factor in macrophages and peripheral blood mononuclear cell cultures and chemotactic responsiveness in lymphocytes [38].

Vallejo [15] documented that, acute and chronic opioid administration have inhibitory effects on humoral and cellular immune response including antibody production, natural killer cell activity, cytokine expression and phagocytic activity.

All these data explain our results, in which we demonstrated that, there are a negative correlation between the level of cytokines and both of age and duration of addiction i.e. chronic opiate addiction had inhibitory effect on cytokine level Table (4).

TNF up-regulates u-opioid receptors in the neuronal cells via the transcription factor.

The broad spectrum of action of cannabinoids on immune functions is thought to result in decreased host resistance to bacterial and viral infections as observed in various experimental animal models. Cannabinoids, especially the major psychoactive component tetrahydrocannabinol (THC) exert immunomodulatory effects that alter normal functions of T and B lymphocytes, NK cells and macrophages in human and animals. The molecular and cellular mechanisms for these effects are not fully defined, however, it appears that receptor as well as non-receptor mechanisms are involved [28,39].

Like opiate receptors, cannabinoid receptors are G-protein-coupled-seven-transmembrane receptors of which two types have been identified CB1 and CB2 [40,41].

CB1 receptors are associated with the brain and certain peripheral tissues and are responsible for behavioural effect of THC, while CB2 receptors are located in the periphery, especially on immune cells [42,43]. The discovery of cannabinoid receptors has led to the identification of a class of endogenous compounds that bind to these receptors,
called endocannabinoids, although the majority of the compounds are eicosanoids [44,45].

Ligand binding to either CB1 or CB2 inhibits adenylylate cyclase, an enzyme that is responsible for CAMP production and is, thus an integral aspect of intracellular signal transduction [46]. Cannabinoids inhibit the rise in intracellular cAMP that normally results from leucocyte activation and this might be the pathway through which cannabinoids suppress immune cell functions [47].

THC displays an exceptional lipophilicity, allowing its cerebral storage, leading to long lasting effects, by far more lasting than its presence in blood, and beyond the period throughout the intoxicated people feel a disablement. This is linked to its slow release from brain areas in which large proportion of spare receptors exists (reserve receptors). This landscape of cannabis urges to make a radical alteration in the public communication about this drug of abuse as it has yet caused so many troubles [48].

Experimental animal studies have suggested that THC treatment causes susceptibility to various infectious agents [49,50]. Disease progression and mortality pathogens were increased on infection with herpes simplex virus and bacterial pathogens such as staphylococcus [51]. These data explain our results in which there are high percentage of respiratory tract infection (Table 2). The host immunity involves many cell types, both immune and non-immune, as well as chemical factors such as cytokines and chemokines and hormones of the HPA axis. Moreover, cannabinoids showed a tendency for heavy use to result in suppression of lymphocyte proliferation [52]. Serum immunoglobulin (Ig) levels were modulated by cannabinoid use, with decreased level of IgG protein and increased levels of IgE protein [39]. However, [40,53] reported that cannabinoids decrease the levels of some cytokines which typically explain our results in which there are decrease in the level of some proinflammatory cytokines. Some cytokines, such as interferon and interleukin 2, are produced by T-helper-1 (Th1) cells. These cytokines help to activate cell- mediated immunity and the killer cells that eliminate microorganisms from the body. Cannabinoids suppress the production of those cytokines, and also they modulate the production of cytokines such as IL1 and TNF and IL6 [54]. In contrast [1] reported that mice receiving a (THC) injection 1 day before and day after a sub-lethal L. pneumophilla infection died of septic shock resulting from production of high levels of proinflammatory cytokines.

Immune cells respond to cannabinoids in a variety of ways, depending on different factors such as drug concentration, timing of drug delivery to leukocytes in relation to antigen stimulation and type of cell function as well as duration of addiction [55] which emphasize the correlation existing in Table (5). When lymphocytes are stimulated by antigen, they first proliferate and then mature or differentiate to become potent effectors cells, such as B-cells that release antibodies or T-cells that release cytokines [6]. The normal T-cell proliferation can be inhibited by cannabinoids [56].

Adverse effects of cannabinoids on immune function have been observed in experimental animals at doses 50-100 times the psychoactive level [57] which explain our results (Table 3). However, in four patients using herbal cannabis therapeutically for over 20 years, no abnormalities were observed in leucoicyte, CD4 or CD8 cell counts [58]. Investigations of multiple sclerosis patients using therapeutic cannabinoids revealed no major immune changes [59].

Cigarette smoking is linked to community – acquired infections and is considered one of the risk factors for respiratory infections [60].

Cigarette smoke is composed of two components, the vapor phase and the particulate phase. The immunosuppressive effects of smoke and nicotine occur in the particulate portion, thus suggesting that nicotine is at least partially responsible for the inhibitory effects on the immune responses [61]. Nicotine is a small organic alkaloid synthesized by tobacco plants and is recognized as the addictive component of cigarettes. Nicotine is an agonist for nicotinic acetylcholine receptors which are present on cells of the CNS as well as other cells through out the body including immune cells [62,63].

The neural nicotinic acetylcholine receptors are upregulated in smokers [64]. Rapid progression of nicotine from cigarette smoke in the lung to the brain increases dopamine transmission within the brain in the shell of the nucleus accumbens, a region essential for reward processing that has been associated with addictive properties of other drugs including opiates, alcohol and cannabinoids [65].

Nicotine appears to affect the immune system through nicotine acetylcholine receptors on cells in CNS and on immune cells similar to opiates and cannabinoids. Nicotine induces glucocorticoids through the HPA axis, that modify the immune
Moreover, nicotine affects immune cells directly [66].

In vitro treatments by nicotine and other extracts from cigarette were observed to inhibit cytokine production [67].

Rodents exposed to cigarette smoke in inhalation chambers have increased susceptibilities to infection: when challenged with aerolized bacteria or viruses [68].

Our findings showed a statistically significant higher percentage of cigarette smokers among addicts compared with the control group (Table 1). This may imply that smoking habit is the first step for drug abuse.

This is in agreement with [69], who reported that smokers had higher rate of drug dependence than non-smokers.

Also, there was a statistically significant difference between addicts and control group as regards respiratory manifestations (Table 2). Cigarette smoking is highly addictive, a puff on a cigarette leads to peak nicotine levels within 10 seconds and dependence is common after as few as 100 cigarettes. Nicotine addiction creates the link between smoking and lung cancer.

Our findings were consistent with [70], who confirmed that nicotine was demonstrated to enhance the growth of L. pneumophila and causes a corresponding inhibition of IL6, INF-a and IL12 in a murine alveolar macrophages cell line through nicotine acetylcholine receptors. In our study, there was a significant elevation of respiratory symptoms detected in our surveyed group compared to control group (Table 2).

The substance also affects murine splenocyte production of cytokines in a differential manner [66,67].

Nicotine has immunomodulatory effects which are apparently receptor mediated [1]. Smoking is often known as the gateway that leads to the use of recreational drugs.

Tramadol is structurally similar to morphine and has both opioid and nonopioid mechanisms responsible for its clinical effects. It is a centrally acting analgesic with moderate affinity for opioid receptors. However, the metabolite o-demethyl tramadol appears to have a higher affinity than the parent compound for the same receptors. In therapeutic doses, tramadol does not appear to produce significant respiratory depression or cardiovascular effects. Most of the analgesic effects are attributed to the nonopioid properties of the drug.

Tramadol may exert its analgesic effect by blocking the reuptake of biogenic amines (e.g., norepinephrine and serotonin) at synapses in the descending neural pathways, which inhibits pain responses in the spinal cord.

Although not related to traditional opioids, tramadol can produce euphoria in some users. At high but therapeutic single doses, tramadol induces a state of well-being. Effects of tramadol such as, increased energy and a significant improvement of symptoms related to depression and anxiety are similar to other opioids but with longer duration due to its complex mechanism and longer half-life [71].

Tramadol is associated with the development of physical dependence and a severe withdrawal syndrome [4].

Tramadol causes typical opiate-like withdrawal symptoms as well as atypical withdrawal symptoms including seizures [72].

Yong-min, et al. [4] concluded that, low dose of tramadol may play a role on cytokine production and increase lymphocyte proliferation.

Moreover, [73] demonstrated an increased tumor necrosis factor TNF-a and prostaglandin E2 concentrations in the cerebrospinal fluids CSF of rats treated with analogics, which is consistent with our results where the level of cytokines (IL6, IL1, TNF(x)) are significantly higher in tramadol addicts compared to the control group (Table 3).

Inhibitory effect of tramadol on phagocytic cell capacity is controversial. However, [74] reported that tramadol does not impair the phagocytic capacity of human peripheral blood cells.

However, cytokines are known to be key players in host response to infection, immunological disorders and tissue injury in the attempt of an organism to overcome the insult and restore homeostasis.

These cytokines are immunomodulatory peptides secreted in very small amount by a variety of cell types, including activated macrophages or monocytes, fibroblastes and endothelial cells [75,76].

When the immune system is fighting pathogens, cytokines signal immune cells such as T-cells and macrophages to travel to the site of infection. In addition, cytokines activate those cells, stimulating them to produce more cytokines.
Tumor necrosis factor α (TNF-α) is the prototypic proinflammatory cytokine as a result of its role in initiating a cascade of cytokines and growth factors in the inflammatory response.

TNF-α exerts its effects through two known receptors, TNFR1 and TNFR2 which are expressed on inflammatory cells [77].

TNF-α regulates a plethora of vital functions in the whole body, under both physiological and pathophysiological conditions [78].

TNF as well as IL1 and IL6, have major systemic effects when either produced acutely in large amounts, as in case of bacterial sepsis, or chronically in lesser amounts, as in the case of chronic infections [79]. IL1 and TNF are extremely potent inflammatory molecules. High concentrations of the proinflammatory cytokines, IL6 and TNF are found in patients with acute meningococcal infection [80,81]. All these facts explain our results in which we found a statistically significantly elevation of the cytokines among tramadol addicts compared to control group (Table 3).

There are an interaction of IL-1, IL-6 and TNF, in human T-cells [69].

IL-6 is an interleukin that acts as both a proinflammatory and anti-inflammatory cytokine. It is secreted by T-cells and macrophages to stimulate immune response to trauma, especially burns or other tissue damage leading to inflammation, but, in terms of host response to foreign pathogen, IL-6 has been shown, to be required for resistance against the bacterium, streptococcus pneumoniae [82].

IL-6 is one of the most important mediators of fever and of the acute phase response. It is capable of crossing the blood brain barrier. Intranasal administration of IL-6 was shown to improve sleep-associated consolidation of emotional memories [83].

IL-1 can trigger fever by enhancing prostaglandin E2 (PGE2) synthesis by the vascular endothelium of the hypothalamus and can stimulate T-cell proliferation. In addition, IL1 elicits the release of histamine from mast cells at the site of inflammation [79].

Conclusion and recommendation:

Drugs of abuse are immune-modulators. Opiates and cannabinoids addiction lead to decreased levels of IL1, TNFα, IL6. Tramadol likely has a natural role in immune-modulation. However, the role of tramadol in immune system is multi-faceted and remains unclear. So, further researches should rely upon the variety of mechanisms through which tramadol can influence human immunity and even physiology to limit its wide use.

References

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