Patients’ Views on the Differences between Three Types of Methadone Syrups in Iran: A Qualitative Study

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Running title: Differences between Methadone Syrups in Iran
Abstract

Objective: This study was designed to compare the methadone syrups produced by three different pharmaceutical companies from the perspectives of patients and other concerned individuals.

Materials and Methods: A qualitative study was conducted via content analysis. Through purposive sampling 26 substance abuse patients were selected and interviewed through focus group discussions. Other concerned individuals included: clinic nurses (3 persons), drug experts in the ‘Substance Abuse Office’ of medical universities’ ‘Food and Drug Administrations’ (2 persons), opiate drugs stock-keeper (1 person), clinic physician-technicians (2 persons), and, methadone retailers and brokers (2 persons). The latter underwent in-depth semi-structured interviews. Upon analysis the data were classified, coded and thematically grouped.

Results: The extracted codes were classified into four main themes:
1. Physical characteristics: syrup color, odor, taste and consistency.
2. Therapeutic effects: onset of effect, potency and duration of effect.
4. Opinions, feelings, thoughts and emotions following syrup change: apprehension of unfamiliarity, upset about change without prior notice, unpleasant feeling about constant changes, feeling disrespected, feeling deceived, feeling of being imposed.

Conclusions: In a nutshell, patients’ dissatisfaction of the physical characteristics and mode of changing syrups was very prominent. The latter was also thought to have less potency and maintenance one of them as opposed to another. In addition to the low consensus on the drug’s side-effects, it is basically very difficult to attribute such effects to a specific pharmaceutical product when different products are used interchangeably.

Keywords: Methadone Syrup, Methadone Maintenance Treatment, Patient Compliance, Adherence to Treatment, Qualitative Study.
Introduction
Methadone is a powerful agonist of µ opioid receptors, and has pharmacologic effects similar to morphine (1, 2). It is the first drug used in maintenance therapies for opioid dependencies (3, 4). Although other drugs have been created for this purpose methadone is still the drug of choice in this mode of therapy (5).
The long-term use of this drug is relatively harmless (6), and is a suitable drug for maintenance therapy in its oral form because of its slow onset of action and long half-life. It can help reduce opioid drug abuse and eventually reduce crime and prevent the spread of infectious diseases (7-9).
In Iran, the drug comes in forms of 5, 20 and 40mg tablets, a 5mg/ml syrup, and a 10mg/ml injection (The standard form of the syrup is 1 mg/ml in other countries; the thinner form of the syrup makes its injection practically impossible). So, unlike other drugs, its injectable form has no place in the treatment of addiction.
The methadone syrup is manufactured by three pharmaceutical companies in Iran. The off and on distribution of these syrups by the food & drug administration of the country’s medical universities has created certain problems in maintenance therapy and patient compliance.
One of the aspects of a successful therapy is patient compliance. Not only does patient non-compliance lead to bad therapeutic results, but it will also lead to wastage of financial resources etc. Earlier studies have shown that 30-70% of patients diagnosed with a chronic disease do not practice appropriate adherence to their treatment (10, 11).
Multiple factors have been said to be involved in patient compliance, some of which are: patient-physician relationship (12), satisfaction of results and various aspects of treatment (13), and side effects of treatment (14). Moreover, patient compliance is related to the severity and quality of the disease, and the psychological & psychiatric well-being of the patient (15). Patients non-compliance toward medical advice and treatment may be attributed to many reasons, such as, wrong beliefs about the effectiveness of treatment, occurrence of difficulties during the course of treatment –such as side effects or financial limitations (16, 17), the need for other family members’ support (18).
According to Simpson (1984) and Hubbard (1997) the duration of treatment is an important predicting factor in the treatment of substance abuse (19-21). Earlier studies also show that compliance toward the physician’s advised treatment, dose and instructions is largely dependent on the ability to correct addiction habits and behavior –based on the patient’s beliefs and learning (19-22).
Resistance to change pathological behavior is another major factor in patient non-compliance. People who enter the substance abuse rehabilitation program are usually in the initial inactive phases of change. Concepts like denial, temptation and regress, walking out of treatment and (addiction) recurrence (particularly in outdoor patients) explain this resistance (20, 23-27). The most likely time the patients may leave the program and avoid adherence to the treatment as a result of non-compliance is the initial phases of treatment. Patients who are in the pre-change phase may also leave the program (28).
A study on treatment compliance in chronically ill patients conducted by Shrank et al (2006) showed that patients’ beliefs and information greatly affected their compliance toward the prescribed treatment with generic and commercial drugs (29).
One of the problems associated with the methadone maintenance therapy has been the reluctance of a large proportion of patients toward taking one of the Methadone syrups. Most patients believe one of them has a lower quality than its counterpart produced by another.
This study was therefore designed to scientifically evaluate this claim, and if necessary correct this wrong belief through educational mechanisms. Hence, this study was conducted to compare the methadone syrups produced in Iran from the perspectives of patients and other concerned individuals.

Materials and Methods
A qualitative study was conducted through content analysis and inductive reasoning (30). Through purposive sampling substance abuse patients visiting three clinics applying maintenance therapy with agonist drugs were selected and interviewed through focus group discussions (FGD). The patients had been on maintenance therapy for the past 18 months and had used at least two types of methadone syrups. Eight to twelve subjects were chosen for each group (31-33). Furthermore, other concerned individuals who were somehow involved in the process of treatment were also selected: clinic nurses (3), drug experts in the ‘Substance Abuse Office’ of medical universities’ ‘Food and Drug Administrations’ (2), opiate drugs stock-keeper (1), clinic physician-technicians (2), and, methadone retailers and brokers (2). The latter underwent in-depth semi-structured interviews. Notes were also taken during the interviews. All participants read and signed the consent form and gave permission for voice-recording.

The data collection tools included a checklist and an open questionnaire. At the beginning of each session, the interviewer would explain the objectives of the study and then the members of each group would narrate their personal experiences regarding the subject at hand. Moreover, a questionnaire was completed listing the participants' individual properties for each participant. Upon initial analysis, the data were classified, coded and thematically grouped (34). Based on Graneheim & Lundman’s method, conventional content analysis was used to analyze the data (35).

To ensure external validity of our findings and credibility of data, the following techniques were applied: full engagement, allocation of adequate time, good communication, accurate and elaborate descriptions (all the details given by the participants were written). To ensure trustworthiness (the equivalent of internal validity in quantitative studies) three well-known techniques (36-39) were used:
1. Member check: the participants are asked to assess the overall findings and comment on their authenticity.
2. Analytic comparisons: raw data are looked up to compare and assess the theoretical framework with the raw data.
3. Audit mechanism: two qualitative research and content analysis experts supervised the stages of coding, conceptualization and extraction.

Results
Over nine hours of FGD and in-depth interviews were held with 26 patients and 9 concerned individuals. The study population’s age ranged from 22-58 years (mean=39.46 years). Upon grouping and deletion of similar cases, the extracted codes were classified into 4 main themes.
1. Physical properties
Patients are very sensitive to the physical properties of syrups and it seems to be one of the main criteria for judgment and opinions of patients. The patients’ opinions were classified into four sub-themes:

1-1. Color: One of the syrups was initially produced as greenish yellow and now is very light yellow to colorless. Second syrup is colorless and the other is reddish. The first characteristic a patient notices a change in the syrup is its color. It seems that the different color of syrups has had certain consequences.

1-2. Odor: Once the syrup colors were similar, this characteristic caught more attention. Apparently, one of the syrups has a vanilla-like odor, which makes it different from the other types.

1-3. Taste: The main physical and obvious difference between the syrups was their taste. In addition to their particular odors, this characteristic was the main differentiating factor between the three, which triggered the participants’ positive and negative comments about the drug and about compliance.

1-4. Consistency: The consistency and thickness of the syrup is another characteristic the patients notice and take into consideration in their judgment.

2. Therapeutic effects
This theme included 3 sub-themes:

2-1. Onset of effect: Although the pharmacologic and pharmacokinetic properties of each drug is clear and stable, these properties somewhat differ in productions of different brands and consumers’ biologic conditions. These differences are the basis for patients’ judgments about the syrup they use.

2-2. Potency: This is the result of methadone’s adherence and tendency toward μ receptors.

2-3. Duration of effect: The patients interpreted this property as the drug’s ‘longevity’ which is affected by the drug’s half-life and clearance from the body. The effectiveness of two syrups differed from the patients’ perspectives, ranging from dissatisfaction to satisfy. A large number of patients liked the oldest syrup of Iran’s MMT program for its long-acting. Some of the patients believed there was not much difference between the syrups, or at least they could not tell.

3. Side effects
This theme consists of 8 subthemes. Some patients believed some of the subthemes were more prominent in one syrup and less prominent in the others. Some thought they were equally prominent in all syrups.

3-1. Generalized problems: Weight loss, lethargy, weakness and weariness were not prominent in any syrup.

3-2. Sleep disorders: sleep deprivation, excessive sleeping, sleepiness and drowsiness, uncomfortable sleep, interrupted sleep, etc. are among these disorders. There were more complaints of one of the syrups.

3-3. Gastrointestinal: A wide range of methadone’s side effects were observed here, such as: dry mouth, constipation, diarrhea (resulting from less substance abuse or its weakened effect), nausea and vomiting, gastric pain and cramps, changes in appetite. Patients’ views were very different; although they were relatively more satisfied with oldest syrup than others.
3-4. Cardiac – Respiratory: No reported.
3-5. Dermatologic: No reported.
3-6. Sexual: A major portion of the dissatisfaction with methadone may be attributed to its sexual side effects, particularly reduced sexual drive and comes with all kinds of syrup.
3-7. Neurologic-muscular disorders: In both group there were.
3-8. Psychological: No reported.
Most patients had experienced and reported at least one or two of the subthemes of side effects. Only a few could differentiate between the three syrups and their associated side effects.

4. Opinions, feelings, thoughts and emotions following syrup change:
The fourth theme consists of six subthemes.

4-1. Apprehension of unfamiliarity
For example: “I think, what if my syrup changes... it might make me less high, and then, craving and lapsing... all return. This is what scares me and make me hangover.” Patient 19

4-2. Upset about change without prior notice
For example: “You’re taken aback when you suddenly come and see that your drug has changed. It stupefies us.” Patient 19

4-3. Unpleasant feeling about constant changes
For example: “There should be single syrup. Or there should always be three. For example, the yellow shouldn’t be unavailable when I like it. Such changes were really unpleasant. This way I’ll go after the substance.” Patient 11

4-4. Feeling disrespected
For example: “I was kinda offended. I felt as if they were giving us a lower quality drug instead of what they should be giving us. It is disrespectful.” Patient 20

4-5. Feeling deceived
For example: “When I got the new syrup and went home to use it I felt the taste had changed, and didn’t like it. I thought maybe the doctor thought it better not to tell me. I felt kind of deceived.” Patient 22

4-6. Feeling of being imposed upon
For example: “I felt it was forced upon us. Like, the yellow one was imposed upon us. I even thought of going out to buy my own medicine and finding the white methadone.” Patient 18

Discussion
Based on the results of the study, the patients and other concerned individuals’ opinions were classified into 4 main themes. The first and fourth themes contained strikingly significant points. On the other hand, the other two themes (drug effects and side effects) contained somewhat unreliable and conflicting statements. It seems that more accurate studies are required in these fields to confirm these findings.

There was a high consistency among patients and other concerned individuals opinions regarding the syrups’ physical properties, such that their positive and negative points were highly reliable. The most outstanding aspect of this theme was unpleasant taste and odor of two brands, as opposed to third. Apparently, such properties are detectable by patients in long-term treatments and hence, it is important to suit the therapy to their palate to achieve better compliance results.

The other two physical properties of the syrup i.e. its color and consistency have been noticed
by the patients and have triggered mixed reactions; even walking out of the treatment has ensued.

Anyhow, these syrup changes and properties have affected the patients, and seem to arise from their previous backgrounds based on their beliefs, teachings and experiences and their resistance toward change. The result of the aforementioned reactions is non-compliance. Earlier studies have also shown that a patient’s resistance toward changing pathological behavior, beliefs and imaginations based on personal experience and teachings are among the main factors contributing to non-compliance (20, 23-27).

Apparently, if the management team gives the necessary information and explanations about the therapeutic approach and instructions to the patient, his compliance will improve. Moreover, it has been shown that the physician-patient relationship is one of the influential factors in raising patient compliance in long-term treatments of chronic diseases (12).

The second theme extracted is the therapeutic effects of the drug, comprising the ‘onset of effect’, ‘potency’ and ‘duration of effect’. This theme seems to contain a wide range of opinions and conflicting statements. In many instances the patients’ judgments about the syrups seem to be based on their previous impressions and somewhat affected by their own preferences of what the syrups should be like. Moreover, it seems that the patients are unable to compare the onset of effect of the three syrups (by recalling their past experiences).

Some patients were not able to differentiate between the three syrups qualitatively at all. Some patients, however, thought one type of the syrup was better.

Examining the therapeutic effects and potency of the drug and what is termed by the patients as its ability to make them ‘high’ & its longevity are largely possible through chemical analysis.

The third theme consists of eight subthemes, upon which there was little consensus. Here too there was much variation and conflicting statements. Some patients attribute a specific side effect (SE) to specific syrup. However, these results have not been addressed by other patients as well. Secondly, most patients have experienced more than two SE at different timings, which make it very difficult to differentiate between the timing of the SE and the type of syrup taken. What’s for sure is that many SE appear after a long time of using a drug, and the time of onset of an effect is hardly detectable, nor is the drug that is possibly responsible for that SE. Mostly, the duration of intake and dose of a drug affect the occurrence of side effects, rather than the brand type. Since two types of syrups had been taken for a much shorter duration than the other type, caution must be taken in attributing the side effects to them alone.

Another point that must be kept in mind is that the drugs can be purchased outside the clinic easily, and many patients have done that several times. The drugs available in the black market are many a time mixed with other abused substances such as benzodiazepines and tramadol. So the occurrence of SE becomes complicated when other drugs and impurities enter the cycle of maintenance treatment.

It is very likely that this patient’s reduced sexual drive is a consequence of methadone itself, and not that of the type of syrup. Upon looking up patients' file we found that their daily methadone dose had increased over the past few months.

Reduced sexual drive in methadone-using patients was mostly observed in married individuals. Another issue that causes spousal dissatisfaction is premature ejaculation, which usually exists in such patients. This too can contribute to men’s reduced sexual drive (40-43). Moreover, single men’s acquaintances with different persons of the opposite sex, their
numbers of partners and their recent experiences are other reasons why their sexual drive reduction differs from that in married individuals. Upon personality evaluations, drug abuse patients have shown to have novelty and sensation seeking temperaments (44-47). Since this temperament trait affects all their pleasure-seeking activities, the difference in sexual drive can also be explained.

The last theme extracted from patient interviews was their ‘opinions, feelings, thoughts and emotions following syrup change’, which was further classified into 6 sub-themes. Like the first theme, there was much consistency between patients’ feedback and responses. They all felt unpleasant about the drug change and particularly that it was done without prior notice. Almost all felt bad and dissatisfied with this aspect of the treatment.

All the subthemes of this theme are concepts that can greatly be reduced if the service-providing team holds counseling sessions and psychotherapy in order to change their behavior and compliance to treatment.

Based on literature, addict patients have certain behavioral problems, such as poor cooperation (44), which can affect their compliance in treatment. The more the patient is aware of the treatment procedure, the possible problems that may arise, and the more he self-reflects, the greater his incentives for treatment and better his compliance toward it (48). However, the findings of the fourth theme all point toward the absence of the aforementioned phenomena.

This qualitative research is the first step toward identifying patients’ interests in different types of methadone syrups. No doubt this is just the beginning, and it cannot provide a basis upon which long term decisions are made. This study can light up the path for more accurate and quantitative studies in the future. An important part of our findings directly or indirectly hint toward low awareness among patients, physicians, nurses and other concerned individuals, be it in general knowledge or specialized knowledge.

Conclusion
Patients’ dissatisfaction from the physical characteristics of most recent syrups was more than the older. Also their dissatisfaction from ongoing changes in mode of distributing Methadone syrup was very prominent and significant. Keeping them in the dark about the drug change and its compulsory nature has negatively affected them. Patients were also less satisfied with new products of this drug in terms of potency and longevity as opposed to their older counterpart. However, a closer look at the participants’ conflicting statements somewhat reduces the reliability of these findings. Further quantitative studies can throw light on these findings.

Furthermore, there is less consistency in the opinions expressed about the drug’s side-effects. Hence, it is very difficult to attribute such effects to a specific pharmaceutical product when different products are used interchangeably. Totally and currently –for whatever logical or illogical reason- the older products that have been distributed since the beginning of the MMT program in Iran is more wanted than the other types.

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Conflict of Interest
There is no conflict of interest. Pharmaceutical companies had no role in the design and conduct of the study; collection, management and analysis of the data; or preparation, review and approve of the manuscript and as is clear in article, there is no bias in their favor in results.
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