

### **Benzodiazepine: Slow sand of Addiction**

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#### **A case vignette:**

"43 years old zamindar from Punjab, Pakistan, presented in a psychiatry clinic with increasing restlessness, palpitation, shortness of breath, insomnia since 3 days. Symptoms became pronounced after stopping all medications, prior to consultation. Upon seeing the psychiatrist, he insisted on intravenous (I/V) injection of Valium. When informed about the hazardous effects of prolonged benzodiazepine use, Mr NB was quick to point out that previous physicians were quite liberal in the use of requested medication. In fact his last physician has prescribed Tab. Alprazolam (2 mg) three times a day, besides intravenous, Valium 10 mg, once or twice a week.

NB started using Tab. Alprazolam (0.5 mg), once in a while, four years ago, on advice of a 'friend', who was a Doctor. This was due to a psychosocial stressor; many years after the marriage couple had no issues. Work-up revealed that he has 'Azospermia'. This stressor was subsequently buried under the pile of investigations by general physicians, internists and gastroenterologists. He carried a 'thick folder' containing reports of endoscopies, echocardiograms, ECG's besides repeated Biochemistry investigations. He was prescribed various compounds from the benzodiazepine group, always with the reassurance that nothing is 'wrong' with him.

He was diagnosed to have Somatoform disorder — undifferentiated type and benzodiazepine dependence syndrome. Subsequently he was advised admission for Detoxification and Management of this iatrogenic complication."

#### **Background**

In the context of Pakistan, a developing South Asian country, cases like these are norm rather than an exception. Physicians prescribe these medications indiscriminately, without supervision. To add to the problem, in the absence of robust legislation and its lack of implementation, benzodiazepines are available over the counter; they can be acquired without any one asking any questions. Alprazolam, is one of the benzodiazepine which is registered and available over the counter by around 20 trade names. Unlike Pakistan, Benzodiazepines are enlisted as controlled drugs (CDs) in the United Kingdom (UK) and

therefore supply is regulated by the Misuse of Drugs Act.1971. Although, legislation surrounding the supply and management of CDs was fairly stringent before the Shipman incident, post-Shipman inquiry has tightened the legislation even more.<sup>1</sup>

This problem has multiple facets; health care system related factors, legislation and economic factors contribute to the overall burden of problem. Some of these would be highlighted in this review.

In Pakistan, there is a dearth of properly trained and qualified psychiatrists (in all, 320). The psychiatrist to population ratio is dismally low. In a recent World Health Organization (WHO) facts sheet it was estimated to be 0.2/100,000. Most of these professionals are centered in urban areas. Almost 67 % population resides in rural areas to which mental health care is delivered by general physicians. Prevalence estimates of common mental disorders is about 30% - ranging from 10-to-25% in urban settings to 30-to-66% in rural settings.<sup>2</sup>

Tranquilizers have become an accepted component in the lives of a large segment of our population. By a conservative estimate around seven to ten million urban dwellers in Pakistan continue to consume these medications regularly. Most of these medication are available over-the-counter without any medical prescription.<sup>3</sup>

#### **Benzodiazepines misuse:**

The most commonly used tranquilizers are Pharmacological compounds called Benzodiazepines. Not only in Pakistan but around the world benzodiazepines are among the most prescribed and consumed medication groups. The discovery of first Benzodiazepine, Chlordiazepoxide, in 1957 by Leo Stern Bach was a landmark in modern psychopharmacology.<sup>4</sup> Chlordiazepoxide was soon followed by a large number of similar compounds, which were quickly introduced in clinical practice, becoming among the most successful drugs ever introduced.

Various compounds from the group of Benzodiazepine are available in the market. They are marketed with various attractive names and labels; it is not uncommon to see adjectives like tranquility, serenity and relaxation intertwined in the names of some compounds.

These seductive labels are heinous efforts to sell the drugs. The existence of Benzodiazepine dependence was described in the early sixties with very high dose of chlordiazepoxide but it has become a real concern for the medical community since the late seventies with increasing number of reports of withdrawal symptoms.

If this is not enough, benzodiazepines are the most favored medication of self-harm. In the context of Pakistan, this has stemmed from their status as sleeping pills; in an overdose one would expect a person to 'sleep forever'. Favorably their pharmacological lethality index is very high. However this in no way makes them any less dangerous than other drugs of overdose.

### **What does local research tells us:**

If we look at the research carried out in developed countries, Benzodiazepine overdose is the most common way of self-poisoning among the substance induced suicidal attempts, accounting for about 40% of the total. A study done in Germany reports this proportion to be 32%. The study also reveals that 80% of the drugs used in self-poisoning were prescribed by physicians' themselves.<sup>5</sup>

In a study done in Pakistan the proportion of Benzodiazepine usage in deliberate self harm, it was more than the double quoted in the western data i.e. 80%.<sup>6</sup> However the predominant method of getting these drugs was their availability over the counter in 44% cases, the fact which can be safely generalized to almost all developing nations.

In the context of Pakistan general physicians prescribe these medications with great fervor, with out educating the patients regarding the potential for dependence and abuse. In a general survey of visitors coming to Aga Khan University Hospital, a group of 7 medical students inquired about the knowledge, awareness and practices related to benzodiazepines.<sup>7</sup> Among 475 participants' 38% reported current use of one or the other compound; 68.3% used them for sleep, 52.2% for stress or anxiety, 10.9% for Ghabrahat, 7% for depression, 0.8% for fits and 10.2% for other reasons. On inquiry 85% participants reported that these medications were prescribed by Physicians at some point in time. Among these Physicians 60% were general practitioners.

During this survey it was discovered that around 80% people were aware of one or more brand of benzodiazepines - available over the counter. Among these 67% had some idea that if these medications are used for a longer duration than they can become a liability. It was noted that their potential for dependence and subsequent abuse was a major concern.

In another cross sectional survey, exploring the point

prevalence of benzodiazepines use at a tertiary care hospital in Karachi, another team of seven medical students randomly selected and interviewed 205 patients. The point prevalence of the benzodiazepines was 21.2%. Prevalence estimated in Psychiatry inpatients were 62%.<sup>8</sup> Another study exploring help seeking behaviour in psychiatric out-patients detected a point prevalence of around 22%.<sup>9</sup>

A cross sectional of Medical students at Aga Khan University, exploring attitude and awareness towards drug use, showed some concerning opinions. A large majority of them was tolerant towards self-prescription of benzodiazepine for short term use. Though these drugs might be helpful in short term alleviation of stress, they nevertheless can lead to serious consequences.<sup>10</sup>

In order to understand the growing problem of benzodiazepine use, we have to explore various market forces, which continue to perpetuate this menace.

### **Economics factors:**

According to one estimate psychotropic drug sale in Pakistan for a duration of one year (June 2003-4) were worth 2.76 billion; of these tranquilizers and hypnotics were 1.36 billions with a rising trend of 18% and 137% respectively from previous year.<sup>11</sup> Situation is not any different in UK. Department of Health data reports that General Practitioners in England wrote 12.7 million prescriptions at a cost of £20.9 million in 2002, compared to 15.8 million prescriptions worth £13.8 million in 1992. 30% of prescriptions were for 56 or more tablets. People over 65 years received 56% of prescriptions for the three most commonly prescribed benzodiazepines.<sup>12</sup>

In the context of Pakistan Pharmaceutical companies, driven by economic gains, marketing these tablets as absolute recipe for peace of mind. Most Physicians act as 'agents' for sales and promotion; with their share in the cake. Health care in the private sector is an industry and is driven by the 'profit motive.' Ipso facto, hospitals are less an instrument for providing relief from suffering than money-making machines. The position of medical profession, by and large, is no more, to put it in kind words, a noble profession; self-serving motives dominate. Ultimately it is the patients and their families who have to pay the cost - be it the lavish luncheons in five star hotels or cruise trips to exotic location. This is obviously done in the guise of science, technology and promotion of 'robust' evidence

Government spends less than 1% of GDP on health care.<sup>11</sup> Hospitals in public sector do not exist to the needed measure and existing ones are understaffed and undernourished with regard to doctor-patient ratio (which results in care-less mood of doctors), medicine and

diagnostic tools. The masses have no option but to be let exploited by the hospitals in private sector. As it is an issue pertaining to masses, it is not a national issue; Islamabad, capital of Pakistan is five miles away from Pakistan and due to this remoteness, those who matter feel, as research in human behavior reveals, no moral qualms in inflicting pain on masses by not regulating and monitoring private hospitals.

### Possible solutions:

Any possible solutions have to keep in mind the clinical as well as public health perspective to this problem. In UK, it is deemed a 'good practice' as not to prescribe or dispense the Benzodiazepines for more than 28-day. Though GP's can prescribe the drug for a longer duration, patients need to be cautioned regarding the potential for addiction. Those who have developed the Dependence syndrome need to be referred to specialists or Substance abuse clinic. The National Institute of Clinical excellence (NICE) guidelines offers practical directions on clinical use of Benzodiazepines.<sup>13</sup> In general, the three rules that apply to benzodiazepine are that prescribing should be kept to a minimum, reviewed regularly and discontinued as soon as possible.

A public health approach to the menace of benzodiazepine dependence should focus at multiple level; primary, secondary and tertiary prevention strategies should be designed. Following recommendations can be helpful in curtailing the problem of Benzodiazepine misuse:

- ◆ Arrange Public awareness program
- ◆ Organize regular C.M.E programs involving G.P's
- ◆ Develop Good practice guidelines for drug prescription
- ◆ Better Drug regulation and dispensing mechanisms
- ◆ Need to develop and implement Legislation
- ◆ Early recognition and referral to mental health services

- ◆ Need to establish well staffed Rehabilitation centers.

Though we are at a cross-road of managing the fall outs of Benzodiazepines use, it is important to have a re-look at their clinical utility. Those who are using these medications find themselves in the slow sand of Addiction. If this situation is to change, then information needs to be disseminated to all stakeholders.

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