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Adverse drug reactions in psychiatry outpatients: Clinical spectrum, causality and avoidability

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ABSTRACT

The present study was done to study the clinical spectrum of Adverse Drug Reactions (ADRs) and determine their causality and avoidability in patients attending Psychiatry Out patient Department. A prospective observational study over a period of one year (from June 15, 2011 to June 15, 2012) was carried out in the Department of Psychiatry, Victoria hospital. ADRs in patients attending Psychiatry OPD were recorded, irrespective of the diagnosis, using Central Drugs Standard Control Organization (CDSCO) suspected adverse drug reaction reporting form and causality assessed using WHO-UPC causality assessment criteria. ADRs with certain, probable or possible causal relation was considered for analysis. Avoidability was assessed using Granada schema for determining whether drug related harm can be avoided. Data was analyzed using descriptive statistics. A total of 329 patients were screened for ADRs, out of which 67 ADRs were reported. Of 67 events recorded, 61(91.04%) were probable and 6(8.96%) were possible. 21 different types of ADRs were noted, most common being tremors (19.40%), extrapyramidal symptoms (14.93%), insomnia (10.45%) and weight gain (7.46%). Majority of ADRs were noted for antipsychotics (38.88%) followed by antidepressants (35.82%) and antiepileptics (13.42%) with olanzapine (16.41%), chlorpromazine (10.45%) and amitriptyline (8.96%) causing most ADRs. Rare events like clozapine induced delirium, olanzapine induced oculogyric crisis and risperidone induced perioral tremor were noted in our study. A wide spectrum of ADRs including some less frequently reported events were noted in this study. Results are comparable to similar studies conducted in India and abroad.

Key words: Adverse drug reaction, Psychiatry, causality, avoidability

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INTRODUCTION

An Adverse drug reaction (ADR) is defined by World health organization (WHO) as a “any response by a drug which is noxious, unintended and occurs at doses normally used in man for prophylaxis, diagnosis, or therapy in turns it may give such hazards effect for a fatal life.” [1] Each year there are 1.5 million hospitalizations caused by ADR in the United States accounting for 5% of hospital admissions and 5% of hospital deaths, making them fourth to sixth leading cause of deaths and drug related injuries in hospitalized patients. [2] It is seen that 52% of these among outpatients and 45% among inpatients are preventable. [3] According to the WHO, the cost of ADRs in the general population is high and under-reporting by health professionals is a well-recognized problem.

According to the National Institute of Health and Family Welfare in India, about 2 -3 % of the population, suffer from seriously incapacitating mental disorders or epilepsy and about 10.4 - 53% visiting the general OPD are

diagnosed with mental disorders. CNS disorders have been estimated to account for up to 20% of the nationwide cost of healthcare in the developed countries. Various survey projections indicate that sales of drugs to treat neurological diseases and other CNS drugs will approach more that $70 billion and that expected to approach up to $ 225 billion in next five years. [4]

Most of the psychiatric illnesses need long term or even life- long therapy, making the patients more prone for the development of significant ADRs and decrease patient compliance. Olfson et al reported that around 42.4% of patients discontinue antidepressants within 30 days mainly due to specific adverse effects. [5] Off-label use, combination therapies and newer indications for older drugs have lead to change in the ADR profiles of many well known psychotropic drugs. The well known AMSP (Arzneimittelsicherheit in der Psychiatrie) study concluded that the incidence of severe ADRs among psychiatric inpatients were about 1.5%. [6]

Growing public concern over drug safety has stressed the importance of pharmacovigilance, especially in India where ADRs contribute to significant economic burden. The Institutional pharmacovigilance programme of Bangalore Medical College and Research Institute has been working in this regard to monitor, detect, assess and disseminate the ADRs which ensures patient safety and minimizes the costs of healthcare. Although spontaneous reporting system is the core of data generation in pharmacovigilance, active drug surveillance increases the detection of ADRs and adds to its benefits. Active monitoring done by the physician following prescription of drugs is also an important way to improve rational drug prescribing. [1] Hence this study has been taken up to supplement the institutional pharmacovigilance programme and improve our knowledge on the pattern of ADRs in psychiatric patients in our hospital.

EXPERIMENTAL SECTION

This was a prospective observational study carried out in the outpatient department (OPD) of Psychiatry, Victoria hospital. The study aimed at analyzing the clinical spectrum of ADRs in psychiatric patients, and determining their causality and avoidability. It was a part of ongoing pharmacovigilance programme in the hospital and had necessary clearance from hospital authorities.

Patients diagnosed with a Psychiatric disorder using ICD10 criteria and being treated with one or more pharmacological agents who attended the OPD between June15, 2011 to June 15, 2012 were screened for ADRs, irrespective of the psychiatric diagnosis. Patients who were not alert or oriented enough to give a detailed history and not accompanied by an attendant, those who were under the influence of alcohol or any other abusive agents and those patients who were not willing to give an informed consent were excluded from the study.

Four psychiatry postgraduate students and one pharmacology postgraduate student who were trained in recording ADRs, recorded the events using Central Drugs Standard Control Organization (CDSCO) suspected adverse drug reaction reporting form. After taking an informed consent from the patient and the attendant, patient's demographic details, relevant past and personal history, findings of general and systemic examination, diagnosis, treatment, laboratory investigation reports, ADR details including the nature of reaction, date of onset, severity, treatment given, outcome, suspected drug including its dose, pharmaceutical form, route of administration, list of concomitant drugs, over the counter drugs and their details were recorded. A senior psychiatrist was available for consultation in situations of ambiguity. Patient interview and examination, interviewing the patient's attendant and previous outpatient and inpatient records and prescription slips were the source of information. Causality of each adverse event was assessed using World Health Organisation – Uppsala Monitoring Centre (WHO-UMC) causality assessment criteria. [7] The ADRs with certain, probable and possible causality were considered for analysis. Severity of ADRs was assessed by Hartwig's Severity Assessment Scale. [8] According to it, an ADR is termed mild if it did not require change in the treatment or required withdrawal of suspected drug however no antidote or specific treatment was given or did not prolong the hospital stay. Moderate ADRs required withdrawal of suspected drug and specific treatment, and led to admission or prolonged hospital stay by one day. Severe ADRs required intensive medical care or caused permanent harm to the patient or led to death of the patient. Avoidability of ADRs was assessed using Granada scheme for determining whether drug related harm can be avoided. [9] According to it, drug related harm is considered avoidable if it occurred due to nonprescription of preventive treatment, unnecessary medicament, prolonged therapeutic ineffectiveness, and drug interaction, poor patient compliance, under or over treatment, inappropriate duration of treatment, incorrect self medication or error in drug administration on part of the patient.

RESULTS

A total of 329 patients were screened for ADRs out of which, 67 patients were suspected of having atleast one ADR. Among them, 43 were males and 24 were females. Age group of study subjects ranged from 12 to 76 years with the average being 43.49 years. Distribution of study subjects according age and gender are given in [Table 1].

Table 1: Age and gender distribution of the study subjects

Age groups	Males	Females	Total
0 – 10	0	0	0
11 – 20	2	1	3
21 – 30	7	5	12
31 – 40	8	7	15
41 – 50	9	2	11
51 – 60	12	5	17
61 and above	5	4	9

Schizophrenia (26) was the commonest clinical diagnosis among the study patients followed by depression (12), bipolar disorder (11), epilepsy (4), obsessive compulsive disorder (4) and others (10). 23 patients had other significant medical illnesses like diabetes, hypertension, cardiac disease or chronic kidney disease and their respective medicines were also recorded.

Central nervous system was commonly affected by ADRs, followed by musculoskeletal, metabolic, dermatological and anticholinergic side effects in the present study. Twenty one different types of ADRs were noted in the study [Table 2], with tremors (13) being the most common, followed by extrapyramidal symptoms (EPS) (10) and insomnia (7). Some infrequent ADRs like Clozapine induced delirium, Olanzapine induced oculogyric crisis and Risperidone induced acute dystonia (perioral tremor) were noted during the study. Antipsychotics were the most common drug class associated with ADRs among which atypical antipsychotics were implicated in 14 cases. Antidepressants and antiepileptics were the other classes of drugs commonly associated with ADRs in this study. [Graph 1] Olanzapine was commonest offending drug, followed by Chlorpromazine, Amitriptyline and Lithium. [Table 3]

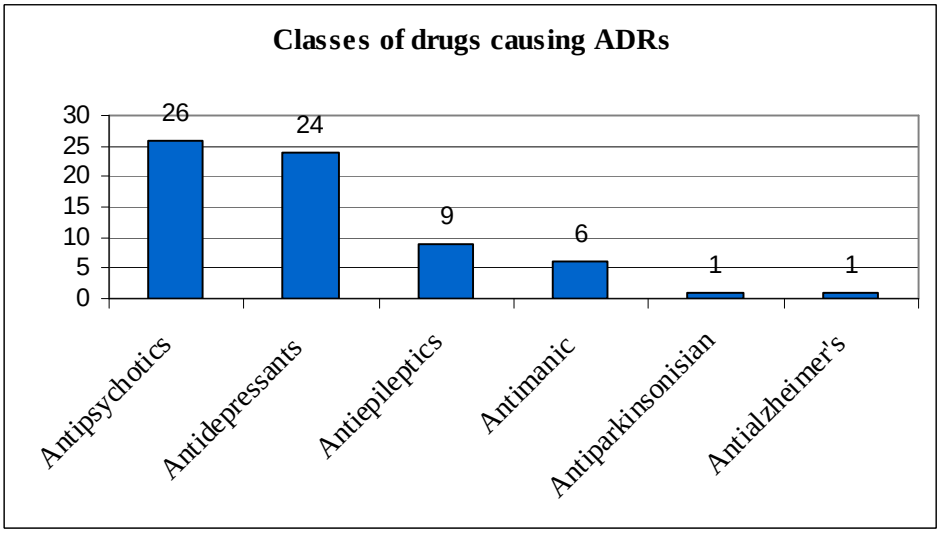
Table 2: Adverse drug reactions noted in our study

Adverse drug reactions	Number of cases (percentage) n=67
Tremors	13 (19.40 %)
Extrapyramidal symptoms (1 Tardive dyskinesia, 1 perioral tremor, 1 oculogyric crisis, 3 akathisia, 4 acute dystonias)	10 (14.93 %)
Insomnia	7 (10.45 %)
Weight gain	5 (7.46 %)
Anxiety	5 (7.46 %)
Constipation	4 (5.97 %)
Irritability	3 (4.48 %)
Dryness of mouth	2 (2.99 %)
Alopecia	2 (2.99 %)
Anemia	2 (2.99 %)
Hyperglycemia	2 (2.99 %)
Nausea	2 (2.99 %)
Steven Johnson Syndrome	2 (2.99 %)
Delirium	1 (1.49 %)
Diarrhea	1 (1.49 %)
Retention of urine	1 (1.49 %)
Agitation	1 (1.49 %)
Muscle cramps	1 (1.49 %)
Maculopapular rashes	1 (1.49 %)
Somnolence	1 (1.49 %)
Toxic epidermal necrolysis	1 (1.49 %)

Table 3: List of suspected drugs causing ADRs

Suspected drugs	Number of ADRs
Olanzapine	11 (16.41 %)
Chlorpromazine	7 (10.45 %)
Amitriptyline	6 (8.96 %)
Lithium	6 (8.96 %)
Sertraline	5 (7.46 %)
Fluoxetine	5 (7.46 %)
Haloperidol	4 (5.97 %)
Imipramine	4 (5.97 %)
Carbamazepine	4 (5.97 %)
Risperidone	3 (4.48 %)
Sodium Valproate	3 (4.48 %)
Escitalopram	2 (2.99 %)
Phenytoin	1 (1.49 %)
Clozapine	1 (1.49 %)
Donepezil	1 (1.49 %)
Levodopa	1 (1.49 %)
Mirtazapine	1 (1.49 %)
Venlafaxine	1 (1.49 %)
Lamotrigine	1 (1.49 %)

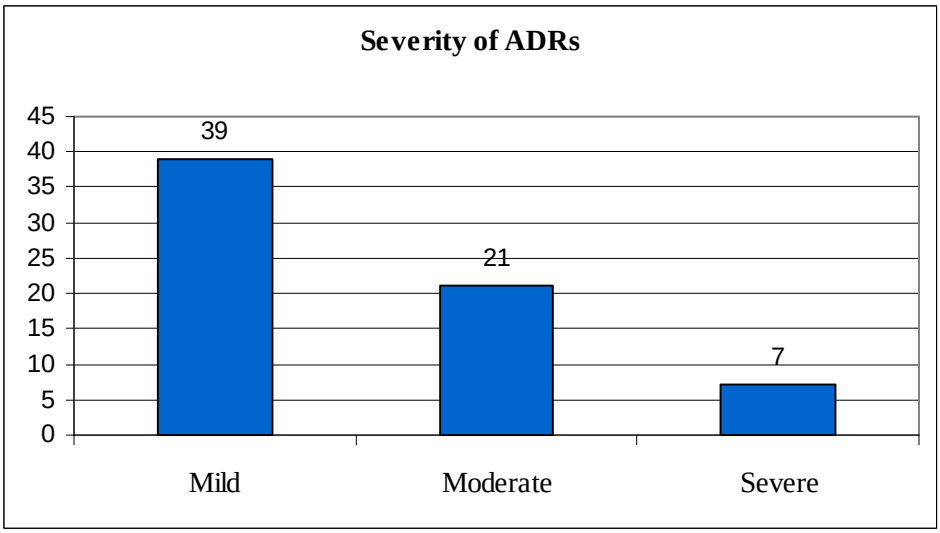
Graph 1: Classes of drugs causing ADRs



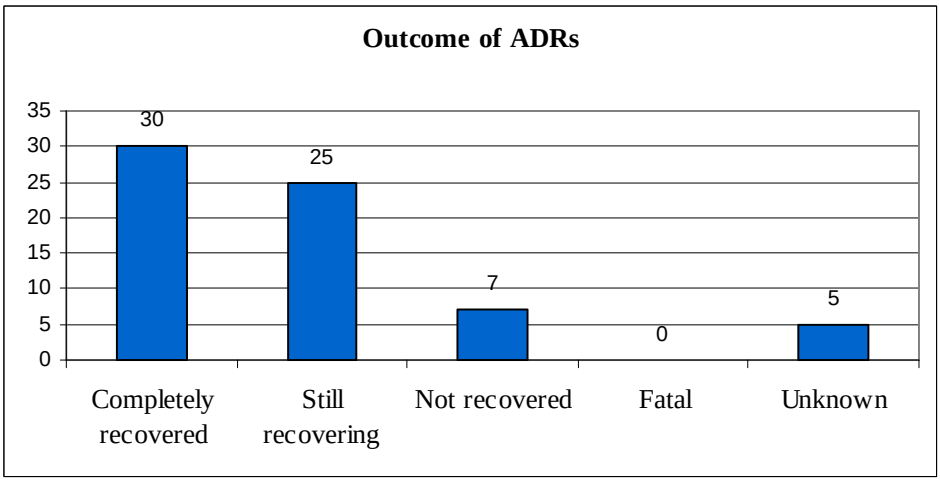
According to the WHO-UMC criteria, 61 ADRs were probable and 6 ADRs were of possible causality. None were named as certain, as rechallenge of the offending drug was not attempted. Most of the ADRs (39) were classified as mild as patients tolerated them well and required no medical treatment except for dose reduction or treatment with alternate drugs. 21 ADRs were moderate, as they required medical treatment along with dosage changes or alternative treatment. 7 ADRs were severe, which required hospitalization and intensive medical treatment. [Graph 2]

Treatment of ADRs is summarized in [Table 4]. Out of 67 cases 30 patients recovered completely and 25 patients were still recovering during subsequent follow ups. But 7 cases did not resolve completely even after treatment and 5 cases were lost for follow up. No deaths or cases of permanent disability were noted during the study. [Graph 3] Avoidability assessment showed that out of 67 ADRs, 29 ADRs (43%) could be avoided with adequate patient advice, legible prescription, timely and appropriate treatment. 4 ADRs could not be evaluated due to inadequate data. [Graph 4]

Graph 2: Severity of the ADRs noted in this study



Graph 3: Outcome of the reported ADRs



Graph 4: Avoidability of the ADRs reported in this study

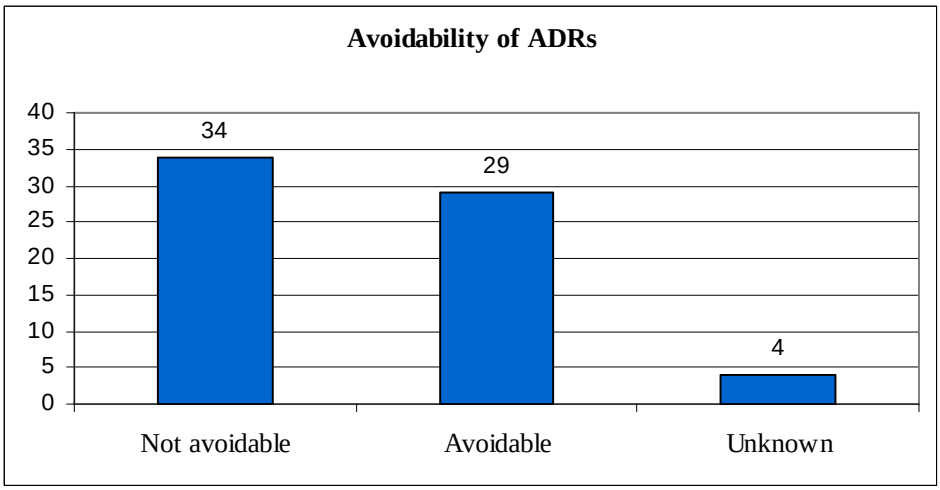


Table 4: Treatment of the ADRs in this study

Treatment given	Number of patients
Continue with suspected drug and reassurance	29
Dose reduction of suspected drug and reassurance	6
Minimal medical treatment and continuation of suspected drug	20
Change of suspected drug to an alternative	6
Hospitalization and symptomatic treatment (with or without change in treatment)	7

DISCUSSION

ADRs are a significant determinant of successful patient treatment especially, in Psychiatry where long duration of therapies is common.

The incidence of ADRs in our study was 20.36% which is similar to a study conducted at Kolkata. [10] Among the study patients, 64.17% were males and 38.82% were females. About 55-60% of patients attending psychiatry OPD in our hospital in any given day, are males which might have contributed to this result. Most common age group reporting ADRs was 51-60 years, followed by 31-40 years of age. A similar study conducted in Pondicherry, noted highest incidence in 21-30 years and attributed this to more number of patients of this age group included in the study. [11] It is well known that, frequency of ADRs is most in extremes of age, but this was not the case in our study as the number of cases in these age groups was comparatively less.

Central nervous system was commonly affected by ADRs, which is similar to that seen in a study conducted in Brazil. [12] Since, most of the psychotropic drugs have effect on central nervous system parameters, this was an expected outcome.

Antipsychotics and antidepressants were the most commonly prescribed psychotropic drugs in our hospital. Antipsychotics were responsible for most ADRs followed by antidepressants, in the present study. This was similar to the study conducted by Sengupta et al and Lohan K et al. [10, 11] Chlorpromazine (high incidence of tremors and EPS) and Olanzapine (high incidence of weight gain and metabolic side effects) were the commonest antipsychotics prescribed and both these drugs are known to cause high incidence of ADRs. [13] Fluoxetine and Escitalopram being the commonest antidepressants prescribed are known to be well tolerated. [14] This could be the reason for higher incidence of ADRs with antipsychotics in our study. Olanzapine tops the list of offending drugs followed by Chlorpromazine and Amitriptyline. Weight gain was the commonest ADR reported for olanzapine (4 cases) which is similar to a study conducted by Lieberman et al. [15]

Among the 21 different types of ADRs noted in our study, tremors and EPS were frequently reported. Both these ADRs are known to be caused by antipsychotics, which is frequently prescribed in our hospital. This is in contrast to a study done by Shah et al, where drowsiness and constipation were the most frequent ADRs, as Tricyclic antidepressants were commonly prescribed. [16]

Among the antidepressants, Selective serotonin reuptake inhibitors (SSRIs) were most commonly associated with ADRs, followed by Tricyclic antidepressants (TCA). This is in contrast to the AMSP study, where TCAs were commonest offenders. [6] This could be due to a newer trend of increased prescription of SSRIs which have a selective action on serotonin reuptake unlike TCAs. Amitriptyline was most commonly associated with ADRs, followed by Fluoxetine and Sertraline. Anxiety and insomnia due to SSRIs were the most common ADRs caused by antidepressants in this study which again denotes its increased prescription. Uher et al reported dryness of mouth, drowsiness and insomnia as commonest ADRs for antidepressants, due to increased prescription of TCAs. [17]

Causality assessment of ADRs in this study showed around 91.04% as probable and around 8.9% as possible with no cases as certain because rechallenge of offending drug was not done. 10.44% of ADRs were termed as severe, which is very high compared to the AMSP study where upto 1.5% of Psychiatric inpatients experienced severe ADRs. [6] Intensive monitoring and timely intervention for ADRs in case of inpatients, which is absent in outpatients could be the reason behind this. This highlights the importance of active surveillance for ADRs in outpatients and requires motivating the patients for regular follow up, which might aid in the early detection of ADRs. Atleast 7 patients required hospitalization due to ADRS. However, no deaths were reported during the study.

Avoidability assessment showed 43.22% of reported ADRs were avoidable. Most of these were due to non-prescription of a preventive treatment, inadequate patient education or inappropriate self medication. This is in contrast to the study conducted in Boston, where only 13% of ADRs were termed as preventable. [18] This indicates that there is a great scope for preventing significant number of ADRs in psychiatric outpatient of our hospital by appropriate and timely prescription of preventive treatment and adequate patient education.

Some infrequently reported ADRs like olanzapine induced oculogyric crisis, risperidone induced perioral tremor and clozapine induced delirium were of particular interest in our study. Oculogyric crisis is an acute dystonic reaction caused due to dopamine inhibition in the striatum, which is more common with typical antipsychotics and in general lesser with atypical antipsychotics. There are only two reports of olanzapine induced oculogyric crisis from India. [19, 20]

In the present study, we noted a 38 year old female diagnosed with schizophrenia on olanzapine 15mg/day since 2 months, presented with rolling up of the eyeballs, restlessness and stiff neck for 10-20 minutes in a day since 3 days. Later, olanzapine was withdrawn and was treated with 50mg of promethazine intramuscularly. Symptoms resolved within half an hour. On discharge she was started on risperidone 2mg/day and trihexyphenidyl 2mg/day.

Perioral tremor or rabbit syndrome is due to a hypercholinergic state resulting from the neuroleptic blockade of dopaminergic neurons in the extrapyramidal system, commonly seen with high potency typical antipsychotics. Although few cases of atypical antipsychotics causing perioral tremor are reported, the incidence is less. [21] A case of risperidone induced perioral tremors was reported in our study. A 57 year old male with schizophrenia, on risperidone 8mg/day for a month, developed twitching of muscles around the mouth, difficulty in talking and moderate drooling of saliva for a week. Risperidone was temporarily withdrawn and was treated with trihexiphenidyl 2mg intramuscular injection followed by trihexiphenidyl 2mg/day orally. The reaction resolved completely within 2 days and risperidone was restarted at 2mg/day.

Clozapine induced delirium was another rare case reported in our study. Delirium due to clozapine is hypothesized to be due to its anticholinergic properties. [22] It can occur in upto 10% of cases being treated with clozapine, and yet is grossly underreported as many physicians may not be aware of such a possibility. [23] Restarting clozapine even after a short drug free interval has been known to trigger delirium and one such case was reported in our study. [22] A 31 year old male patient, a case of resistant Schizophrenia, being treated with 300mg/day of clozapine, had discontinued treatment without consulting a physician for about 2 months. He then restarted the medication at the same dose. The next day he developed confusion, restlessness, irritability, agitation and an attack of seizure. He was hospitalised, clozapine was discontinued, managed with haloperidol, lorazepam and supportive treatment. He recovered completely, and discharged with clozapine 25mg/day.

About five patients who reported ADRs were lost for follow up and their outcome could not be assessed. This could be one of the limitations in our study.

CONCLUSION

A wide range of ADRs including some less frequently reported events like clozapine induced delirium, olanzapine induced oculogyric crisis and risperidone induced perioral tremor were reported in this study. The pattern and frequency of ADRs were comparable to similar studies conducted in India and abroad. However, more number of ADRs in our study were avoidable by simple measures, indicating the scope for improving awareness regarding ADRs. An active pharmacovigilance programme is the need of the hour in any hospital especially in Indian setup, as they cause significant burden to the patients and also to the economy.

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