Isotretinoin (Accutane; Hoffmann-La Roche, Basel, Switzerland) is a drug resembling the chemical structure of vitamin A that is indicated for moderate to severe recalcitrant forms of acne. This lipid-soluble compound affects the central nervous system and reports of intracranial hypertension, depression and suicidal ideation have been published subsequent to its marketing in the USA in 1982 (O’Donnell, 2003).

Although the exact mechanism of action of isotretinoin is still obscure, studies performed in vivo in animals show specific high expression of retinoid receptors and cellular binding proteins in dopamine innervated pathways, especially the striatum, pointing to their possible involvement in the pathogenesis of different psychiatric disorders (Zetterstrom et al., 1999).

Despite serious side-effects and adverse events, the use of isotretinoin in the last 8 years (until 2000) has increased by 2.5-fold (250%), as reflected by the number of dispensed prescriptions (Wysowski et al., 2002).

The growing number of reported cases of depression and suicide associated with isotretinoin use in patients with acne has prompted concern among care givers, as well as among patients and their relatives, and has triggered repeated warnings from government regulators. Recently, the Canadian Medical Association issued a health and drug alert entitled ‘Accutane (isotretinoin) and psychiatric adverse effects’ (Wooltorton, 2003). The reason for posting this alert was the possible link with depression and suicide, as well as the warning that people taking isotretinoin may also experience aggressive and violent behaviour.

The aim of the present report is to add to the growing body of data. We provided a description of five consecutive cases during a 1-year period wherein suicidality and affective, long-standing psychosis occurred within months in young army conscripts after exposure to isotretinoin.
conscripts who were serving their compulsory army service were reviewed at an Israel Defense Forces (IDF) Mental Health Department clinic. The clinic serves as a tertiary care centre.

During the study period, 500 conscripts were seen by a dermatologist for severe acne and the cases described here are drawn from this cohort. There were five cases: two male and three female; mean age 19 ± 1.2 years. All had undergone the draft board assessment before service, at the age of 17 years (Reichenberg et al., 2002).

In brief, the assessment consists of (i) a physical examination, a review of systems and psychiatric history, which were all conducted by a physician; (ii) assessment of language ability; (iii) a battery of tests measuring intellectual functioning; and (iv) a structured interview assessing personality and behavioural traits. None of these screening tests was positive for any of the conscripts before or at the time of their recruitment.

**Results**

Demographic and clinical data for the five soldiers are presented in Table 1.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>Military occupation</th>
<th>Lag time (months)</th>
<th>Predisposing factors</th>
<th>Psychiatric diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>20</td>
<td>Technical sector</td>
<td>3</td>
<td>OCD</td>
<td>Schizophreniform</td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>Technical sector</td>
<td>8</td>
<td>OCD</td>
<td>Suicide attempt</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>Technical sector</td>
<td>7</td>
<td>Family: schizoprenia</td>
<td>Suicide attempt</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>Technical sector</td>
<td>11</td>
<td>Pituitary adenoma</td>
<td>Schizoaffective</td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>Administrative sector</td>
<td>10</td>
<td>Intractable headache</td>
<td>Suicide attempt</td>
</tr>
</tbody>
</table>

*aAll diagnoses were made according to DSM-IV. Lag time = time in months between administration of isotretinoin and development of psychosis. OCD, Obsessive–compulsive disorder.

All five soldiers were treated with isotretinoin for acne prior to the development of psychiatric morbidity. Mean lag time from intake of isotretinoin to occurrence of psychosis was 7.6 ± 4.2 months. In all cases, the psychotic episode had lasted longer than 3 months and, in three of the cases, psychosis lasted longer than 6 months. Manic irritability was noted in all cases. Three of the soldiers had attempted suicide by jumping from a moving vehicle, cutting wrists or administering a self-inflicted abdominal penetrating wound with a sharp object. All received psychiatric treatment, three as inpatients, before their discharge from the army due to their psychiatric morbidity. Psychopharmacological treatment consisted of second generation antipsychotic medications (risperidone in two cases and olanzapine in three cases). Response to treatment was assessed using the 7-point Clinical Global Impression (CGI) scale. In four cases, the response was scored as ‘good’ or ‘very good’ whereas, in one soldier, only ‘very little’ response was observed even after 6 months of treatment.

All patients had a personal or family history of psychiatric or neurological morbidity. In three cases, obsessive–compulsive symptomatology was treated at the age of 16 years. In one case, a pituitary adenoma was treated with decapeptide and another conscript was treated by anticonvulsants due to intractable headache following closed head trauma. In three of the cases, family history revealed a bipolar disorder in a first degree relative and, in one of these cases, a sister had developed a manic episode following isotretinoin treatment at the age of 18 years.

**Discussion**

Isotretinoin is a retinoid that is approved for the treatment of cystic acne, although its indications for use have been constantly extended to include milder cases. There has been a growing interest in the possible association between isotretinoin use and increased risk of depression and suicide. However, this issue remains controversial (Bremner, 2003).

Although case report series are inconclusive, two large retrospective cohort studies, both of them sponsored by Hoffman La Roche, concluded that their results did not support an association between the use of isotretinoin and the onset of depression or psychosis (Hersom et al., 2003).
2000; Jick et al., 2003). Major drawbacks, as well as different interpretations of the results, are presented in a recent review (Hull and D’Arcy, 2003).

Given our observations suggestive of an increase in the likelihood of an association between the development of affective psychosis and the diathesis of the five reported cases, we suggest that screening and identifying those patients who are at high risk of psychopathology is carried out before isotretinoin administration is undertaken, especially in stressful settings such as military service.

References