265 - Benign ethnic neutropenia

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268 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 Risk factors for agranulocytosis include increasing age and Asian race.5 Unlike neutropenia, risk of agranulocytosis appears to be higher in people of European ancestry than in those of African descent.12 Some patients may be genetically predisposed13 (see section on clozapine: genetic testing for clozapine treatment in this chapter). Although the timescale and individual risk factors for the development of agranulocytosis are different from those associated with neutropenia/coincidental low neutrophil counts, it is difficult to be certain in any given patient that neutropenia is not a precursor to agranulocytosis. However, it is notable that only 30% of confirmed cases of agranulocytosis pass through a neutropenia phase during the precipitous fall in counts.12 Haematological monitoring is mandatory to mitigate haematological risk. However, worldwide, there are marked variations in the recommendations for monitoring frequency and the threshold for clozapine cessation,14 reflecting, perhaps, the weak evidence on which they are based. In 2015, the US FDA introduced changes to the clozapine monitoring system making only the ANC mandatory and effectively lowering the threshold for cessation of clozapine treatment.15 It is recommended that treatment with clozapine be stopped when neutrophils fall below 1000/mm16 (compared with UK recommendations for cessation if ANC <1500/mm).16 There is evidence that clozapine is grossly under-used worldwide, with very wide variation in prescribing frequency from one country to another.17 This may be explained at least in part by the stringent blood monitoring requirements. The worldwide outbreak of COVID-19 in 2020 prompted a re-evaluation of clozapine haematological monitoring, with a group proposing a reduction from monthly to 3-monthly for patients who have received clozapine for more than 1 year without a history of neutropenia.18 Implementation of the extended 3--monthly monitoring found no difference in the rates of severe neutropenia compared with monthly monitoring.19 In addition to this, when considering that the development of true agranulocytosis occurs over 10 days or less, the value of monthly monitoring is clearly questionable, especially in patients for whom the overall risk of agranulocytosis is near to zero. Benign ethnic neutropenia BEN is a widely recognised hereditary condition in which the neutrophil count is relatively low – there is a left shift in the normal distribution of counts. People of African or Middle Eastern descent have a high prevalence. BEN is characterised by low WCC, which may frequently fall below the lower limit of normal. This pattern may be observed before, during and after the use of clozapine and very probably accounts for a proportion of observed or apparent clozapine-associated neutropenias and treatment cessation. Many countries allow registration of BEN status whereby different (lower) limits are set for neutrophil counts in these patients. While true clozapine- induced

neutropenia can occur in the context of BEN, evidence suggests that BEN does not pose an increased risk of dyscrasias during clozapine treatment.20,21 The use of genetic testing to identify BEN may be useful in reducing the risk of unnecessary termination of treatment and is strongly recommended for all patients starting clozapine, regardless of ethnicity.22,23

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