ONLINE SUPPLEMENT

Guidelines for follow-up of patients on clozapine

Abbreviations

ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate transaminase
BP	blood pressure
CK	creatine kinase
GGT	gamma-glutamyltransferase
GP	general practitioner
HBA_{1c}	glycated haemoglobin
HDL	high-density lipoprotein
LFTs	liver function tests
NICE	National Institute for Health and Clinical Excellence
USS	ultrasound scan

Metabolic syndrome

Metabolic syndrome, according to the National Education Program Adult Treatment Panel III (NCEP ATP III) criteria, is defined as three or more of the following:

- waist circumference >102 cm (men) or >88 cm (women) triglycerides >1.7 mmol/l
- HDL cholesterol <1 mmol/l (men) or <1.3 mmol/l (women)
- BP >130/85 mmHg
- fasting plasma glucose >6.1 mmol/l.

Patients who develop metabolic syndrome are at significantly increased risk of coronary heart disease, myocardial infarction, stroke, diabetes and decreased life expectancy.[12] This has implications for whether the patient should stay on the drug, and a detailed risk/benefit assessment needs to be made in conjunction with the patient.

Ten-year cardiovascular risk assessment

This is based on data from the Framingham study. Essentially the risk is calculated from five risk factors:

- age
- gender
- smoking habit
- systolic BP
- ratio of total cholesterol to HDL cholesterol.

If the patient has diabetes or heart disease, they are automatically at a much higher risk (see http://cvrisk.mvm.ed.ac.uk).

It is useful to do this assessment at baseline and then yearly to ensure that the risk does not increase too much. If it does increase significantly, then the risk:benefit ratio relating to clozapine may need to be re-evaluated. If the risk is over 20%, then intensive intervention is recommended.

Fasting blood glucose and HBA_{1c}

In 2006 HBA_{1c} was used, and in 2007 fasting glucose was used. Essentially the same path was used, with the removal of the HBA_{1c} part in 2006. This guideline (Fig. DS1) is based on the NICE guidelines for diabetes.[9] The removal of HBA_{1c} is discussed further in the main paper under 'Methodological considerations'.

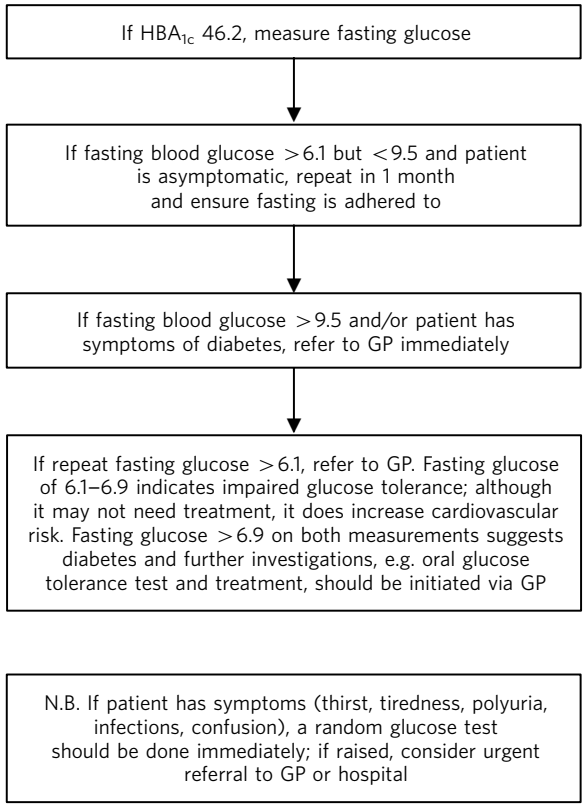

Fig DS1 Fasting glucose and $HBA_{1c.}$

Hypertension

In the NICE guidelines for hypertension, hypertension is defined as persistently raised BP over 140/90 mmHg recorded on three separate occasions.[8] On each occasion the reading should be done twice, once at the beginning and once at the end of a consultation. If either systolic or diastolic BP is raised, referral to the patient's GP is indicated:

- if BP>180/110 mmHg or the patient is symptomatic, immediate specialist referral is needed
- if BP>160/100 mmHg, the patient should be given drug therapy via the GP
- if BP>140/90 mmHg, the 10-year cardiovascular risk should be calculated; if the risk is over 20%, refer to GP for initiation of drug treatment.

Liver function tests

Many patients have asymptomatic raised LFTs. The protocol suggested in the article was drawn up using guidelines from www.gpnotebook.com and after discussion with a hepatologist at the University Hospital of North Durham, and a consultant pathologist at Bishop Auckland Hospital, whose review[12] contained much helpful information.

Asymptomatic raised ALP (1.5–4 × normal)

Asymptomatic raised ALP can be from a bony or hepatic source. It can indicate metastases or Paget's disease if bony in origin, or problems with bile duct drainage, e.g. gallstones or biliary cirrhosis if hepatic in origin (Fig. DS2).

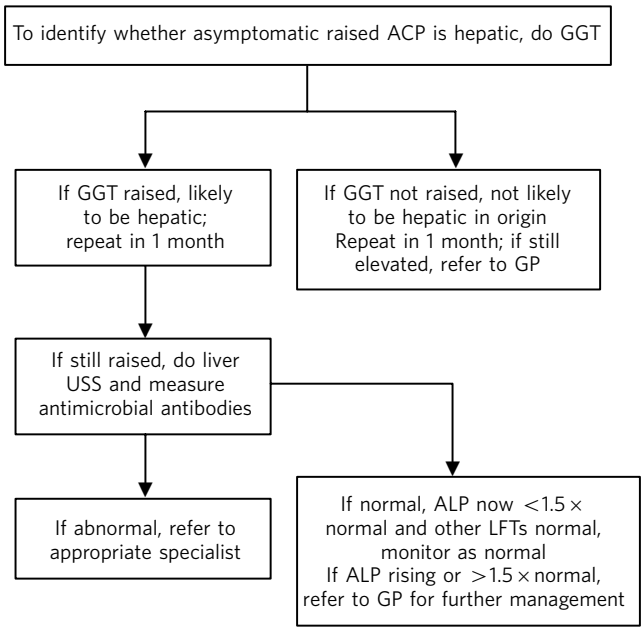

Fig DS2 Pathway for managing asymptomatic raised ALP (1.5–4 × normal).

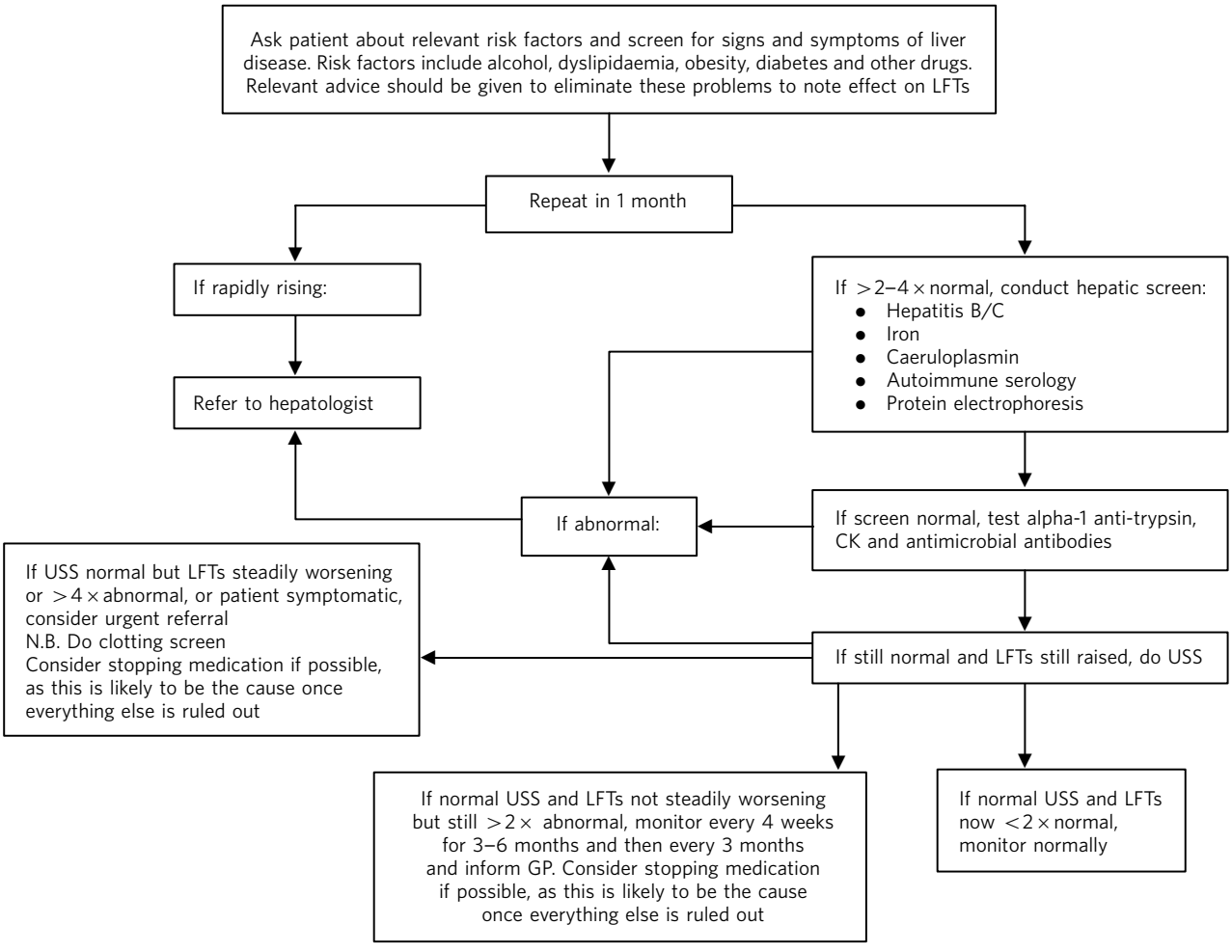

Fig DS3 Asymptomatic AST or ALT (2–4 × normal).

Lipids

This protocol (Fig. DS4) was devised in discussion with a biochemist specialising in lipid management at the University Hospital of North Durham and with reference to the literature.[10,13]

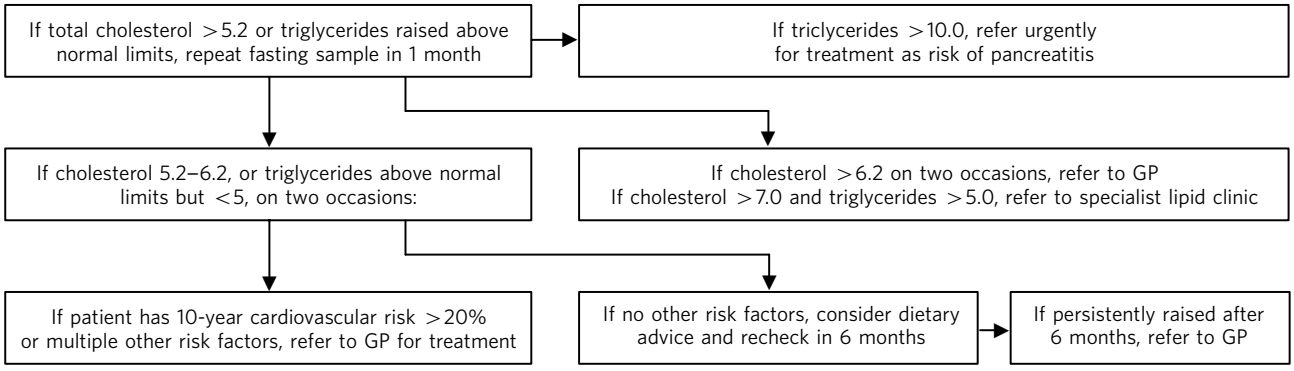

Fig DS4 Pathway for managing lipid results.

Whether a patient gets lipid-lowering treatment depends on the 10-year cardiovascular risk calculations, and so information obtained on this through monitoring is forwarded to the GP with the referral.

Protocol for measuring BP

Hypertension is defined as persistently raised BP over 140/90 mmHg recorded on three separate occasions.[8]

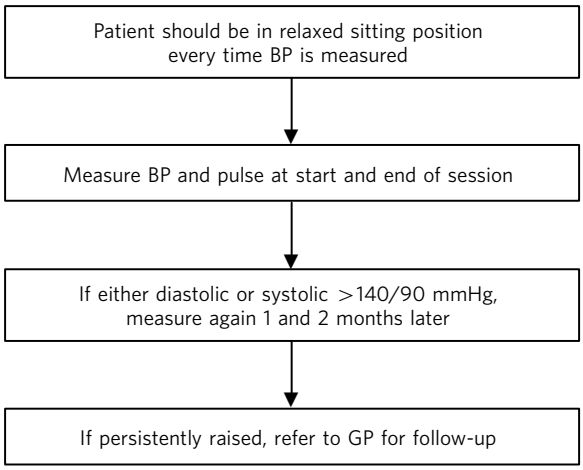

Fig DS5 Protocol for measuring blood pressure.

If BP is over 180/110 mmHg or the patient is symptomatic (e.g. headache, dizziness), refer for urgent medical follow-up.